Alkaline Phosphatase on Sections

Center—Normal Kidney
Left —"Crush" failure
Right —Acute Hypertension

MEDICAL DISEASES OF THE KIDNEY

(An Atlas and Introduction)

by

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FOREWORD

It was in 1914 that Volhard and Fahr published their book on Bright's disease which was at once a monograph and an atlas After thirty five years Dr McManus has given us another atlas and monograph The author is a pathologist with a clinical outlook and a keen appreciation of physiologic and chemical problems His outlook is essentially original and he has studied his microscopic sections not only with the seeing eye but with the understanding mind An admirable balance is maintained throughout between structure function and the manifestations of disease Even a cursory perusal of the text will show how up to date is the treatment of the entire subject The description of the normal histology could not be bettered and it is refreshing to find a morphologist so deeply versed in the chemistry of the cell

An element of novelty is imparted to the work by the extensive use of recent technical methods more particularly the periodic acid—Schiff's reagent stain for bringing out intimate glomerular structure and Gomori's method for demonstrating alkaline phosphatase in the renal tubules Thus figure 87 (hematoxylin and eosin) and figure 88 (periodic acid stain) form a dramatic contrast and demonstrate in a striking manner the value of the latter method for emphasizing basement membranes

However familiar the reader may be with renal structure in health and disease it is safe to say that he will learn new facts and be stimulated to think along new lines by the perusal of these pages and examination of these pictures How many of us for example are familiar with the variations of the position of the Golgi apparatus in the cells of the macula densa under conditions of disease?

These 100 pictures which are a delight to the eye and recall the work of that master of pathologic histology the late F B Mallory tell the whole story of the medical diseases of the kidney

The work appears to be designed for the clinician as much as for the pathologist because the author is not satisfied with demonstrating mere alterations in structure but seeks always to uncover the underlying physiologic and clinical significance of these changes The division of the text into acute renal failure and chronic renal failure is particularly stimulating

Actually a good book needs no Foreword and this is true in the present instance

William Boyd

PREFACE

Do not stop to question whether these ideas are new or old but ask more properly whether they harmonize with Nature And be assured of one thing that I never reached my ideas of the structure of the kidney by the aid of books but by the long patient and varied use of the microscope MARCELLO MALPIGHI— DE VISCERUM STRUCTURA (1666)

THIS is a pictorial introduction to the study of the diseased kidney I have tried to orient the pathologist to the patient and the clinician to the pathology by an alternating discussion of clinical and pathologic details Acute renal failure and chronic renal failure are the two main groupings under which kidney diseases are discussed here These two headings comprise the majority of cases which clinician and pathologist alike encounter

Most of the photomicrographs are taken from sections prepared by the periodic acid Schiff s reagent technique This method demonstrates the renal basement membrane and other carbohydrates in section Its use has permitted the recognition separation and illustration of the process of glomerular injury in arteriosclerosis in pyelonephritis and in glomerulonephritis Tubular atrophy in these three main disease processes is nonspecific but the glomerular changes allow the evaluation of the degree to which each is operating in the diseased kidney studied histologically

The approximation of functional ability in sections of the kidney is possible by the use of Gomori s method for alkaline phosphatase The interpretation of a number of kidney diseases in the light of Trueta s studies on the renal circulation allow a reappraisal of the overall picture in shock and in the crush lesion Including the description of pattern glomerular obsolescence there is much that is new in this treatise

The limited bibliography is explained in part by the newness of the data and concepts Also I have restricted intentionally the references to key articles or first descriptions I should like to mention my dependence upon the standard textbooks of Pathology and the monographs of Bell Fishberg Oliver Addis and Christian for isolated data

Grateful acknowledgement is made to Dr James Miller now Emeritus Professor of Pathology Queen s University Faculty of Medicine Kingston Canada who started my interest in the kidney to the late W G MacCallum and Sam S Blackman Jr who continued it to Drs William Boyd John Fisher J A Cunningham Louis C Posey J D Bush A F Casey Paul Kimmelstiel and others for interesting slides and tissues to John Ledbetter and Edith Gay Jones for the photomicrographs a few being made by Jon Franzke to Sara Howell and her staff of technicians for the sections to Dr Roger Baker Professor of Pathology and my other colleagues of the Medical College of Alabama who have been unsparing with

their help and information to Drs G I Rutledge Jr and R W Mowry who have collaborated in the sections on the Crush Kidney and the Phosphatase studies respectively J C Saunders was associated in the studies of the chemical constitution of the renal basement membrane Miss Charleane Everett did most of the typing Miss Mildred Crowe and her library staff at the Medical College of Alabama have been most helpful A few illustrations have been reproduced by the courtesy of the editors of the American Journal of Pathology the Lancet the Quarterly Journal of Microscopical Science and the Bulletin of the International Association of Medical Museums Credit is given in the legend in each case

A portion of the studies was done on a Beit Memorial Fellowship in Medical Research in the Department of Zoology and Comparative Anatomy the University Museum Oxford At the Medical College of Alabama funds from the Life Insurance Medical Research Fund were used in a study of the histochemistry of arteriosclerosis some results of which are included

J F A McManus

Birmingham Alabama

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Part I. Gross and Microscopic Anatomy in Health

Chapter 1

INTRODUCTION PHYSIOLOGY NEPHRON IN GENERAL

THE normal human kidney can be best understood as a collection of a number of similar units each unit being called a nephron. Supporting these nephrons there is a minimum amount of connective tissue. The one arterial supply and venous drainage nourishes the interstitial connective tissue as well as determining the production of the specific fluid elaborated by the nephron—the urine.

The nephron has a constant number of continuous portions. It begins at the glomerulus a capillary tuft invaginated into the closed end of an epithelial tube. The nephron ends in a large duct system connecting with the pelvis of the kidney. Between the capillary loops of the glomerulus and the collecting tubule the beginning of the duct system the epithelial tubule undergoes a number of contortions. One may recognize in order a proximal convoluted portion a descending loop extending down toward the pelvis an ascending loop returning to the glomerulus of origin about which the distal convoluted tubule is seen to twine before ending in the collecting tubule which receives a number of these distal tubules.

The capillary tuft of the glomerulus delivers a filtrate of blood plasma into the epithelial tube at the beginning of the first or proximal convoluted tubule. A selective process of reabsorption of certain materials and the addition of other substances occurs in the passage of the glomerular filtrate down the tubule to the collecting duct. The duct conveys the final product—urine—to the exterior as represented by the renal pelvis.

In terms of function as well as structure the nephrons appear to be a homogeneous unit group. We have no evidence that the different nephrons do different tasks but it appears that the parts of the individual nephrons possess separate functions.

The efficiency and quantity of the urine production depend in final analysis upon the integrity of the individual nephrons. The acid base balance of the blood the calcium and phosphorous content of blood and tissue the sugar content of the blood the water content of the body and the excretion of many products of metabolism are functions of the kidney and eventually of the individual nephrons. In most of these regulations and controls the kidney represents a single link in a complicated body mechanism but in each the rôle of the kidney is an important one. Disease of the kidneys may be reflected in disturbances of these balances

Besides these chemical relationships with the blood the tissues and the cells of the body the kidney may have an important part in the control of vascular tonus and in regulating blood pressure Changes in the blood pressure more commonly follow diseases of the kidney than of any other organ In many cases of disturbed blood pressure characteristic changes can be found in the kidney

QUANTITATIVE FEATURES OF THE KIDNEYS

Each kidney normally contains between 1 and 1½ million nephrons The glomeruli have a total filtering surface of over twice the body surface area The length of the individual capillaries in a glomerulus totals about 25 mm or 1 inch so that the total of all the loops in both kidneys is about 60 kilometers or 37 miles plus

The kidney at birth has a volume of 6 5 cc There is a gradual increase to the adult volume of 120 cc at about the age of sixteen The diameter of the glomerulus is about 85 mu at birth while the adult glomerulus has a diameter up to 200 mu usually 180 to 190 mu

Some interesting figures (Policard) result from the calculation of total glomerular surface as a function of the body weights glomerular surface in cm per gram of body weight There is a species difference in the length

Mouse	0 458	Pig	0 089
Rabbit	0 144	Human	0 070
Cow	0 06		

of the various segments of the nephrons The loop of Henle is short or lacking in reptiles and in some avians in which a semi solid urine is produced Comparative physiology has not progressed to the point where differences of function can be correlated with differences in structure It may be that the lack of spontaneous glomerulonephritis in animals and the failure of its experimental production may be related to structural differences

THE NORMAL PRODUCTION OF URINE

In twenty four hours about 200 liters of fluid are filtered into the tubules by the glomeruli Nearly 99 per cent of this must be reabsorbed since the daily urine volume is something between 1 and 3 liters The main features of tubular activity are shown in figure 1

It appears fairly definite in the frog and probable in the human that 65 per cent of the fluid is reabsorbed in the proximal convoluted tubule along with all the sugar some of the sodium the phosphate and part of the chloride The loop of Henle has no certain function its variation in length within the kidney from nephron to nephron suggest no constant activity In the distal tubule the remainder of the water is reabsorbed with the rest of the chloride At this level of the tubule the reaction of the urine becomes acid It is now hypotonic suggesting some addition of water

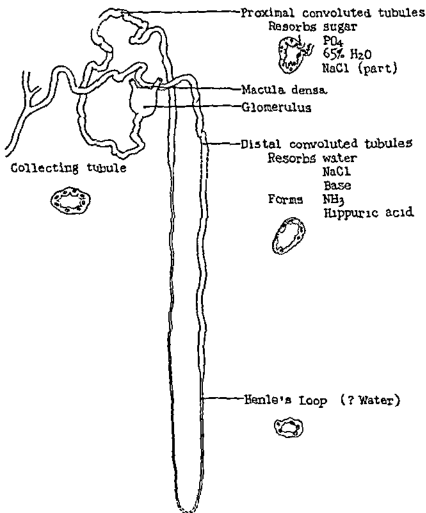


Figure 1

Diagram of Nephron

This diagram shows the continuous portions of the nephron The suspected functions of the portions or levels of the tubule are indicated

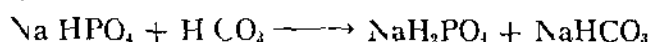
Some of the factors controlling reabsorption are tabulated in the following

Material Reabsorbed	*Site Reabsorbed*	*Controlling Factor*
Sodium	*Proximal Tubule*	Posterior Pituitary Inhibits
Sodium	Distal Tubule	Posterior Pituitary *Increases*
Sodium	Proximal & Distal Tubule	Adrenal Cortex Inhibits
*Water	*Proximal & Distal Tubule*	Posterior Pituitary
Phosphate	Proximal Tubule	Parathormone Increases

The acid base balance has one of *its important regulating* mechanisms in the excretion of urine The fixed base of the body—sodium potassium magnesium and calcium—is preserved by rearranging the balance between NaH_2PO_4 and Na_2HPO_4 The filtrate of blood plasma formed by the glomerulus has a pH of 7 4 The urine has normally a pH from 5 to 7 with a mean of 6 0 The excretion of an acid urine conserves the base for re use by the body

The proportion of acid phosphate to basic phosphate in the original filtrate in about 1 to 4 in the final urine the proportion is normally 9 to 1 and *may reach* as high as 50 to 1 *in a very acid urine The decrease in* basic phosphate is probably produced by reaction with bicarbonate in the following fashion

$$Na_2HPO_4 + H_2CO_3 \longrightarrow NaH_2PO_4 + NaHCO_3$$



Reabsorbed by tubular epithelium

The reabsorption of the sodium bicarbonate conserves base as does the excretion of organic acids such as uric acid as free acids while they exist in the blood in combined forms The formation of ammonia ion by the kidney epithelium and its addition to the urine serves as another method by which the base is conserved

Ammonia formation largely derives from glutamine rather than from urea The problem of disposal of endogenous ammonia is a complicated *one † In the kidney ammonia is formed* from glutamine by the enzyme glutaminase Some of the ammonia may be formed as well from amino acids and from adenosine phosphate Ammonia formation and excretion by the kidney is a defense against acidosis since the acid urine appears to be one stimulus for NH_3 formation

Certain features of urine volume must be remembered for the later appreciation of the changes of disease The normal twenty four hours of output of urine ranges from *1000 to 3000 cc with the day to night proportion* ranging from 2 to 1 as high as 4 to 1 The increase of night urine production is called nocturia Polyuria is the term used to describe any increase in urine production Oliguria denotes decrease in urine volume while anuria describes complete cessation of urine production

* The reabsorption of water in the distal tubule is variable or facultative according to posterior pituitary control (Smith)

† cf discussion in Peters [85]

The specific gravity of the urine usually ranges in health as high as 1 015 or 1 025 and as low as 1 001 after fluid ingestion of high quantity The production of urine of specific gravity equivalent to blood plasma—1 010—is called isosthenuria * The meanings of hypersthenuria as in diabetes and hyposthenuria in some renal disease will be understood easily

THE NEPHRON IN GENERAL

The Glomerulus —The glomerulus of the kidney was first seen by Malpighi[65] some time before 1666 Malpighi was able to inject the glomeruli either from the arterial or the venous side and he described them as resembling apples hung on the vascular tree He believed he had found the glands which secreted the urine but he was unable to see the connections between the glomeruli and tubules to the exterior Bowman in 1842 rediscovered and redescribed the glomeruli as round masses of minute vessels invested by a cyst or capsule The capsule is seen to pass into the basement membrane of the tube as the body of a Florence flask into its neck Bowman suggested part of the modern theory of function when he says It is difficult to conceive the disposition of parts more calculated to favor the escape of water from the blood than that of the Malpighian body

It has already been mentioned that somewhere between 1 and 1½ million glomeruli are found in each kidney The number is constant from birth Each glomerulus has an oval shape and a diameter close to 200 micra The peripheral glomeruli of the cortex are probably larger than the more centrally situated (Peters) Each glomerulus is seen in relation to one afferent arteriole but double (bifid) glomeruli are not too rare in the human

The glomerulus is a tuft of capillaries invaginating the blind end of the tubular portion of the nephron It is in a real sense a capillary bed between the afferent arteriole and the efferent arteriole compactly contorted and covered by basement membrane The capillary tuft of the glomerulus is unique in lacking anastomoses between the capillaries as Vimtrup[66] has shown by injection experiments It would be easy to comprehend the structure of the glomerulus in sections if it were not for the contortions which the capillaries pursue in the elaboration of maximum filtration surface for each capillary The difference produced by contortion can be expressed as AwwwB instead of A——B

The arteriole which gives origin to the capillaries of the glomerulus is called the afferent to distinguish it from the efferent arteriole which drains the capillaries The afferent arteriole connects with a dilated space within the glomerulus the atrium or infundibulum from which the capillaries originate The capillaries course in the glomerulus to terminate directly in the efferent arteriole

The glomerular tuft of capillaries can be seen in the newborn and fetal kidney and in some lower animals to be completely covered by cuboidal

* Isosthenuria also is used to mean fixed specific gravity



Figure 2

Fetal Kidney

This is a low power view of a fetal kidney. The glomerulus is seen as an extremely simple group of capillaries. It is covered by a cuboidal epithelium. The glomerular filtrate if it is formed at this age, is collected in the space of Bowman's capsule and transmitted to the epithelial tubes which are grouped together as parts of the one nephron in the center of the picture.

At this stage of development a basement membrane is present. No reticulin would be shown with appropriate stains except around the larger blood vessels.

This fact demonstrates the independance of reticulin and basement membrane although the two are closely related in adult life (*cf.* pp. 29 31).



Figure 3

Normal Glomerulus Operative Kidney

This is a Bouin fixed portion of kidney removed for a hypernephroma. The capsular space and many of the tubules contain coagulated fluid consisting of carbohydrate and

T

I

affected by clamping the pedicle

2

epithelium In childhood the glomeruli are covered by scarce cuboidal cells In adult life the epithelial covering of the glomerulus consists of scarce flattened cells recognized only in fresh material either from surgical material or early autopsies (Figs 2 3)

The morphology of the epithelial cells covering the glomerular tuft—the visceral layer of Bowman s capsule—has been studied exhaustively by Zimmerman to whom they resemble the Rouget cells of the visceral capillaries [4] With preparations by the DaFano technique for the Golgi element these epithelial cells show a characteristic crab like golgi quite unlike the single globular golgi of the endothelial cells of the capillaries The epithelium covering the glomerulus is continuous with the parietal layer of the glomerular capsule also made up of flattened scarce epithelial cells

Most of the nuclei seen in the usual section of a glomerulus can be seen to derive from the epithelium of the glomerular capsule these epithelial cells outnumbering the endothelial cells of the capillaries by 10 or 12 to 1 The capillaries and their relationship to the basement membrane have been subjects of a considerable amount of study and discussion The description to follow is based upon studies with the periodic acid Schiff s reagent (PAS) method which colors in remarkably selective method the basement membrane [8]

Basement membrane is a histologic term used to describe hyaline thin structures most commonly seen separating epithelium from capillaries Chemically it consists of a protein It contains a carbohydrate moiety as shown by coloring with the periodic acid method and by digestion with hyaluronidase In the glomerulus the relationship necessary for the presence of the basement membrane appears to be the contiguity between epithelium and capillary wall or epithelium and epithelium

It can be seen that the arteriole appears to lose its basement membrane when it enters the glomerulus (Fig 4) and the glomerular capillaries are covered only by the basement membrane of the epithelium of Bowman s capsule The invagination of Bowman s capsule by the capillaries is not so complete as to cover the capillaries entirely with epithelial cells or with basement membrane As a result one sees spaces between the capillaries covered by basement membrane and by epithelial cells (Fig 5) These are the intercapillary spaces about which there has been so much argument The precision of the demonstration of basement membrane with the periodic acid method allows the study of the intercapillary space with a new nicety and the photography of the area previously represented only in drawings

The intercapillary space needs thin sections for its study and it is best seen in lower animals In the dog and cat there may be third cell type—distinct from endothelium and epithelium—in the intercapillary space making up a mesangium or cellular core for the glomerulus In the normal human these cells are scarce or absent and the intercapillary space is best considered to be potential considerably altered in some diseases of the kid

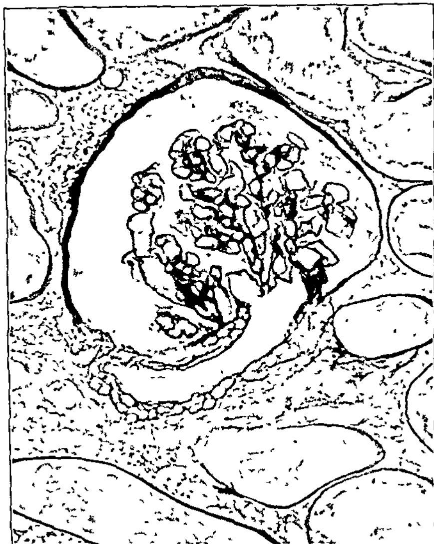


Figure 4

Basement Membrane of the Glomerulus and Tubules

This is a photomicrograph of a section of kidney colored with the periodic acid Schiff's reagent method. This PAS method colors the carbohydrates of tissue. The carbohydrates in the kidney under normal conditions are represented chiefly by the intercellular cement of the arteriole and by the basement membrane of the tubules and glomeruli.

The basement membrane of the glomerulus is seen to be formed from the parietal basement membrane of the glomerulus fusing with the carbohydrate material of the arteriole. The glomerular basement *membrane is then something unique and peculiar to the glomerulus.* The arteriole has some kind of sub-endothelial basement membrane which participates in the formation of the glomerular basement membrane. The basement membrane of the tubules is about normal in thickness or perhaps a little increased. (*McManus, courtesy of Amer. Jour. Pathology.*)



Figure 5

Detail of Glomerulus and Basement Membrane

The basement membrane is colored here by the PAS method The nuclei are stained with hematoxylin It can be seen particularly in the central pair of capillary loops that the basement membrane reflects from one loop onto another This reflection of basement membranes leaves an intercapillary space which is seen in the center of the picture as a "T" space outlined by slightly thickened basement membrane This intercapillary space is important in glomerular disease (*McManus, courtesy of Amer Jour Pathology*)

ney We have not been able to recognize muscle or fibrocytic cells in the normal human glomerulus such as various workers have described in animals and even in human material

The normal glomerulus lacks reticular fibers It consists then as far as can be demonstrated of capillary loops of endothelial cells covered but not invested by epithelial cells The basement membrane of the vessels disappears as the capillaries originate and terminate The basement membrane of the glomerulus appears related to the epithelial cells reflecting over the capillary loops to leave intercapillary spaces

The glomerulus normally fills Bowman s capsule in frozen sections but in the preparation of paraffin sections there is shrinkage so that a space remains between the visceral and parietal layers of the epithelium of Bowman s capsule In disease conditions the space of Bowman s capsule may be obliterated or increased according to the nature of the process It is important however to consider it as a potential space

The filtration surface across which the fluid passes from the blood in the capillary to begin its passage down the tubule in the formation of urine consists of endothelium of capillary the basement membrane and the visceral epithelium There is no evidence that filtration normally occurs into the intercapillary space but there are appearances which suggest that such does occur in disease The features which are essential for normal filtration appear to be the basement membrane capillary and epithelial cells in close relationship As we have seen the reflection of the basement membrane between the loop to form the intercapillary space lacks the essential relationship The part of the capillary wall next to the inter capillary space lacks a basement membrane

The capsular space connects with the proximal convoluted tubule by a narrowed channel of a few cells in length These cells differ from the rest of the proximal convoluted tubule in that they lack the striated (brush) border The cells of the neck frequently show large colloid droplets in their cytoplasm The neck of the glomerulus as it is called is situated at a variable point in the circumference of the capsular space from glomerulus to glomerulus It shows no constant relationship to the vascular pole of the glomerulus The neck frequently is acutely angulated and within a short distance gives over to the characteristic proximal convoluted tubule (Fig 6)

The crucial situation of the glomerular capillaries in the physiology of the kidneys can be understood when it is appreciated that the interstitium of the kidney lacks any proper blood supply of its own The blood of efferent arteriole then furnishes nutrition for the kidney as well as being that to which the material from the tubule passes after reabsorption This mention may be an over simplification of the renal circulation as will appear later but there is general agreement that the renal blood flow is exclusively glomerular or nearly so under normal conditions



Figure 6

A Low Power View of a Section of Cortex

Three glomeruli may be seen in a section The one in the center of the field shows a proximal convoluted tubule leading off from Bowman s capsule A segment of distal tubule rests attached to the arteriole of the glomerulus In the lower portion of the field there are a number of portions of Henle s loops

Representative tubules of various levels are indicated as follows

P proximal or first convolution
D , distal or second convolution
L , loop of Henle

The histologic features of the cells of the portions of the nephron are detailed on pp 23 27

The Proximal Convoluted Tubules —Under optimum conditions of fixation the epithelium of the proximal convoluted tubules nearly fills the space within the basement membrane leaving only a slit like crescentic lumen The basement membrane is hyaline and thick and just internal to it there is a layer of protoplasm or ground substance cementing the tubular epithelium to it There are three or four nuclei seen at the one level of cross section of the tubule Cell margins are seen indistinctly The inner surface of the epithelium the free or lumen surface has a striated epithelial cuticle or brush border With the usual staining methods the cyto plasm is acidophilic and granular Optimum fixation is rare in autopsy material and the epithelium does not ordinarily occupy the majority of the space within the basement membrane (Fig 7)

Mitochondria of rod or batonnet shape can be demonstrated in these cells of the proximal convoluted tubules Normally the mitochondria are arranged as if radiating toward the basement membrane from an imaginary central point There are differences in length of the mitochondria One sees shortened mitochondria with the lumen half of the epithelial cells occupied by granules These granules color with the method used for mitochondria and have been taken to represent a state of function of the tubular epithelium This is not certain There appears to be no relation between the brush filaments of the brush border which can be followed into the cells and the mitochondria

The Golgi element of the cells of the proximal convoluted tubule is relatively large and is placed as a rule surrounding the nucleus or just on the lumen side of the nucleus The changes of the Golgi element in a few diseases have been studied There is no evidence in the human that the Golgi element undergoes a cycle of activity traversing the cell during diuresis such as has been described in some rodents [35]

There is normally no triglyceride fat demonstrable in the cells of the proximal convoluted tubule in the human There are other more com plex lipids in the Golgi element and mitochondria The chromatin of the nucleus can be shown with Feulgen s test to contain desoxyribose nucleic acid There is normally no carbohydrate in the cells except on their brush borders the site of alkaline phosphatase activity This enzyme appears also in the nucleus and to a lesser variable degree in the cytoplasm (Fig 8)

The functional significance of these chemical features of the cells is not plain The alkaline phosphatase is probably related to reabsorption of sugar from the glomerular filtrate but poisoning with phlorizin producing a glycosuria does not remove the alkaline phosphatase A second enzyme a phosphorylase is hypothesized as the one injured by phlorizin This latter enzyme is not demonstrable histochemically at present The de crease of alkaline phosphatase in abnormal kidneys (which will be de scribed later [p 90) is not associated with glycosuria]

Henle's Loop —The descending and ascending portions of Henle s loop are channels of small caliber lined by a single layer of low flat epithelial



Figure 7

A Higher Power Micro-Photograph of Glomerulus in Figure 6

The section is colored by Mallory's Aniline Blue method. The cellular details are well shown, but in the glomerulus other structures beside the basement membrane are colored. This extra coloring makes it difficult to study the finer structure of the glomerulus.

There is a fine brush like appearance for the epithelium of the proximal convoluted tubules on their free surface. This remains sometimes despite serious injury of the tubular epithelium, e.g. the crush lesion pp 87. Fairly frequently the preservation of the brush border is misinterpreted to mean normal epithelium.



Figure 8

Alkaline Phosphatase Preparations, Normal Kidney

This is a photograph of sections of a normal kidney in which the alkaline phosphatase has been demonstrated by the Gomori method Practically all the enzyme is present in the proximal convoluted tubules and restricted to the cortex

This normal appearance should be compared to that in the shock and crush lesions (Fig 18 and Frontispiece) (*Bulletin of International Association of Medical Museums*)

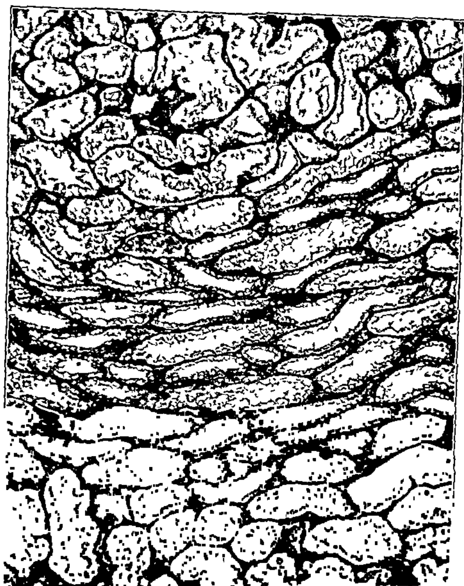


Figure 9

Medullary Ray (Mallory's Aniline Blue)

This is a view of the same kidney as Figs 6, 7, and 10 It shows segments of Henle's loops of several nephrons in the center of the field Above and below is the cortical substance These units constitute a portion of a lobule of the kidney

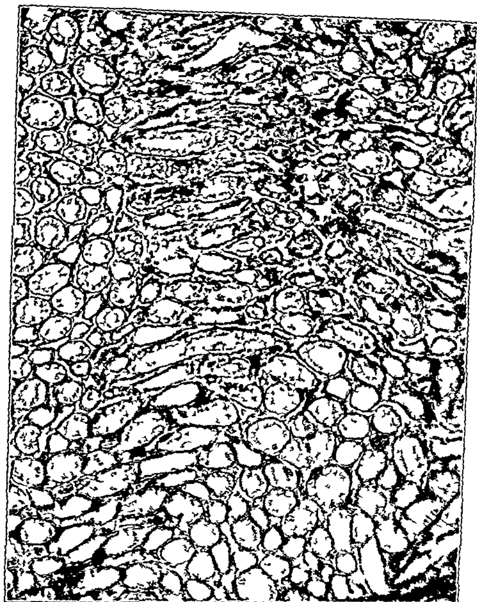
cells The cells are hexagonal in shape and contain only a few granular or filamentous mitochondria The transition from the descending to the ascending limb is not too sharp in terms of structural differences and many continental authorities believe the two portions are of the one structure In the human however the ascending limb is of smaller measure in all details over all diameter size of cells and diameter of lumen

There is no definite evidence that the loop of Henle has any functional activity The paucity of mitochondria in its cells would suggest it does not No demonstrable enzyme activity is seen in the human with the phosphatase methods in the loops of Henle In shock in the rabbit and human certain cells of Henle s loop acquire heavy lipoid in their cytoplasm but the significance of this is unknown

The Distal Second Convoluted Tubule (Figs 6 7 9) —The cells of the distal convoluted tubules are flattened and cuboidal They contain enough cytoplasm to cover their nuclei unlike the cells of Henle s loop in which the nucleus may bulge out the lumen side of the cell The cytoplasm of the distal convoluted tubule cells contains rod like mitochondria somewhat shorter and more delicate than those of the proximal convoluted tubules The mitochondria are usually restricted to the attached half of the cell radiating toward the center of the tubule from the basement membrane

The most important feature of the distal convoluted tubule is the return of the nephron in this segment to the glomerulus of its origin the tubule resting in the angle between the afferent and efferent arterioles There are certain structural peculiarities of this group of cells resting next to the glomerular root In place of the cuboidal cells of the rest of the distal tubule the cells lying against the glomerular root are columnar and there is reversal of their Golgi element A later discussion will detail the histologic and cytologic features of this group of elements at the glomerular root (*cf* p 36)

The Collecting Tubules and Excretory Ducts (Fig 10) —The collecting tubules and ducts are larger channels of increasing caliber lined by cuboidal epithelial cells of relatively simple construction lacking mitochondria and any enzyme activity Many nephrons end or terminate in each collecting tubule the last recognizable portion of the individual nephron being the distal convoluted tubule The insusceptibility of the collecting tubule and ducts to chemical poisons suggests that these structures play an entirely passive rôle The so called uric acid infarcts suggests some reabsorptive function in infants



F gure 10

A Section at the Junction of Cortex and Medulla (Mallory s Anilı ıe Blue)

(*cf* pp 42 During shock a large port on of the cortex s ischem c because of the preferen tial use of these essels

Chapter 2

THE CONNECTIVE TISSUE VESSELS AND NERVES

THE BASEMENT MEMBRANE OF THE TUBULES AND THE RETICULIN OF THE KIDNEY

There is a hyaline basement membrane around each tubule and in and about each glomerulus. In the glomerulus the basement membrane is a part of the filtering surface; its arrangement has been described previously. To repeat, the basement membrane consists of carbohydrate in combination with protein.[77] An inner hyaline portion of the basement membrane has been described as responsible for the adhesion to it of the epithelial cells. The relation of the outer portion to the reticulin fibrils has been studied by many workers, usually repeating the work of Mall.[86]

The fibrils of reticulin form a meshwork about the basement membrane of the tubule and Bowman's capsule. Indeed Mall had considered the basement membrane to be made up of this meshwork of reticulin from this relationship. He found both were digested by pancreatin. However maceration in sodium bicarbonate destroyed the reticulin of the rabbit kidney while leaving the epithelial cells and the basement membrane.

There is no enzyme activity demonstrable histochemically to date in the basement membrane or reticulin. The autolysis of kidney tissue shows the basement membrane to be one of the last structure to disappear. This would suggest the basement membrane is lacking inherent enzyme synthesis. Autolysis is suggested as synthetic enzymatic processes reversed in direction following the law of mass action by the accumulation of metabolites. I do not know of the reticulin being studied from the viewpoint of autolysis. From the ease with which it can be demonstrated long after death it would seem that the reticulin autolyzes slowly and presumably lacks inherent enzyme synthetic activity (Fig 11).

The interstitial spaces of the kidney are filled by ground substance and reticulin fibrils with occasional collagen fibrils. In this regard the interstitial spaces of the kidney resemble in the essential respects those elsewhere in the body. The ground substance consists of a colloidal solution with hyaluronic and chondroitin sulfuric acids as main constituents containing also much of the ingredients of the blood plasma. Imbedded in this viscous fluid are the collagen fibers seen normally only about the vessels and the reticulin fibrils. The latter deserve special mention because of their importance in histology and pathology.

Reticulin fibrils by definition are argyophilic and resist tryptic digestion. These delicate structures terminate on the one hand on the basement membrane of the tubules and Bowman's capsule. Their other connection is in the ground substance between the cells of the vessels. Because of this

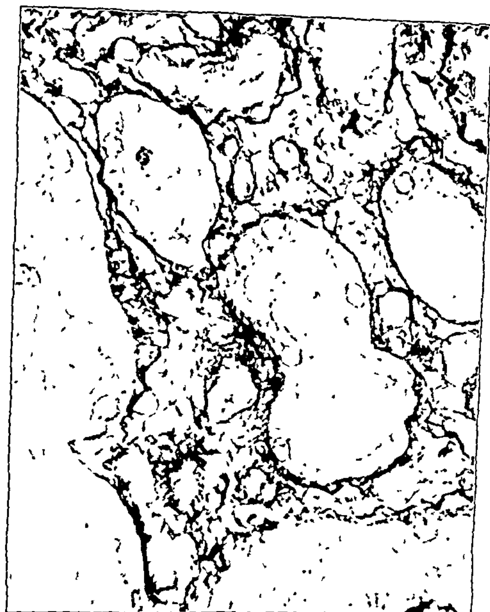


Figure 11

Reticulin Tubules in Cortex

This silver impregnation shows the reticulin as black lines There is some interstitial edema with separation of tubules This allows the intertubular course of the reticulin fibrils to be demonstrated The tubule at the left shows the termination of the fibrils on the tubular basement membrane The other termination (which is not shown) is between the cells of the vessels

connecting position between the parenchyma and the vessels the reticulin fibrils are responsible for maintaining the shape of the kidney Scarring of the kidney means loss of parenchyma with reticulin collapse and rearrangement

The reticulin in embryonic development appears at about the third month and then in relation to vessels At this time the basement membrane is already well defined where tubules exist There is a gradual increase in reticulin between the tubules and the adult form is reached at the end of the first year of adult life Age changes toward collagenization will be discussed later

THE CONNECTIVE TISSUE AND SPACES OF THE KIDNEY

There is normally nothing but reticulin in the connective tissue of the kidney Elastic tissue and collagen fibers are not seen apart from the vessels except in disease It was remarked earlier that the connective tissue of the kidney was small in amount Actually it is only in the pyramids of the kidney that much interstitial space can be seen (Fig 12)

In the space intervening between the collecting tubules and ducts in the medulla and in the pyramids there is a peculiar acellular connective tissue which is remakable for the presence of many capillaries especially at the very tips of the pyramids The aggregate of appearances is remarkable but the function of these structures is unknown The interstitial tissue in the pyramids displays a peculiar hyaline change with aging the material resembling amyloid but not coloring with Congo Red

In the cortex the tubules and glomeruli are clumped together and the space between the units is potential Nothing resembling lymphatic channels can be seen in the normal cortex while the presence of lymphatic channels in the medulla is suggested rather than proven Despite the absence of lymphatics seen in section the probable existence of such channels is suggested by a number of features

Renal lymph can be collected in dogs from large subcapsular spaces at the periphery of the cortex (In abnormal kidneys such spaces are apparent in the human) The renal lymph in dogs seems to have a higher urea content than either the arterial or venous blood It is suggested that the reabsorption from the tubules occurs in the first instance into the interstitial spaces from which it is conveyed to the venous channels by way of the lymphatics I do not know of any adequate demonstration of intrarenal lymphatics in the human but the importance of such a possible relationship and its probability will be discussed

It seems reasonable to suppose that tubular reabsorption occurs primarily into the tissue spaces The tubule is not surrounded by a collar or jacket of capillaries nor can any specialized appearance—morphology Golgi element or mitochondria be seen where the tubule cells adjoin a capillary wall It is unlikely that in the kidney as in other organs re



Figure 12

Loose Connective Tissue, Pyramids

This section shows the intercellular space of the pyramids Several collecting tubules are shown This is one of the few situations in the normal kidney where much connective tissue exists It is a loose almost myxomatous variety In aging this area becomes hyaline resembling amyloid but not staining with congo red

absorption from the tubule passes into the interstitial tissue then into the lymph channel and in turn into the vein

Previously it has been pointed out that the blood supply of the interstitium is derived from the efferent arteriole and represents actually blood which has lost much of its plasma in the glomerular filtration It is only fair to add that the rich blood supply of the juxta cortical portion of the medulla and of the pyramids suggests some additional non glomerular supply for these portions of the kidney

THE BLOOD VESSELS OF THE KIDNEYS

The renal artery supplying each kidney comes off at right angles from the aorta The hydrostatic pressure of blood is maintained by a series of similar divisions until the glomerulus is reached The primary divisions of the renal artery are usually three to five in number The interlobar arteries arise from these A curving set of vessels the so called arcuate arteries branch from the interlobar vessels at the level of the corticomedullary junction They rarely form arches in the human kidney and the term arcuate is a misnomer A series of smaller arteries arise from the primary divisions of the interlobar arteries These pass outward in the cortex to the capsule and are termed interlobular arteries The glomeruli spring from the interlobular arteries by the afferent arterioles only four branchings separated from the aorta and maintaining in the capillaries of the glomerular tufts a blood and filtration pressure only a little lower than the aortic pressure itself (Fig 13)

The larger arteries in the kidney like the main renal arteries are like the aorta in that they are elastic in type — possessing much elastic tissue between the muscular cells of the media The elastica in the media persists in a decreasing proportion until the inter lobular arteries are reached the latter being muscular in type There is relatively little elastica in the media of the arteries of the corticomedullary level (the arcuate arteries) and these arteries are those in which an intimate binding to the reticulin of the kidney is first made

In the interlobar arteries the adventitia is loose while in the arteries of the next order the adventitia directly connects with the interstitial reticulin

The arteries of the kidney are possessed of intima media and adventitia as are arteries elsewhere The important features appear to be a single elastica in the intima and a constant relation of the thickness of the media to the caliber of the lumen These are illustrated in figure 25

The origin of the afferent arteriole from the interlobular artery is the rule but occasionally another short vessel is interposed This vessel is arteriole in type as far as size is concerned but differs in having a media several cells in thickness The usual arteriole contains in its media only one layer of smooth muscle cells limited internally by an elastic lamina

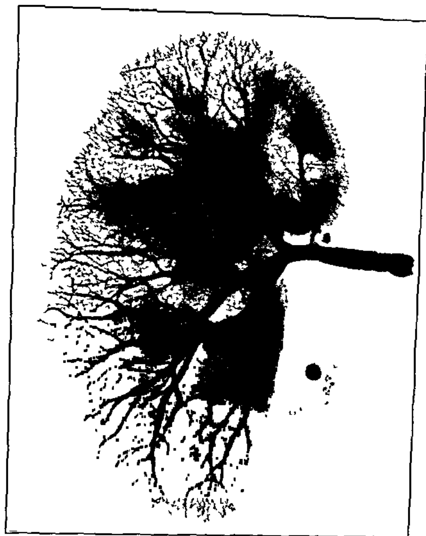


Figure 13

Arterial Supply of the Kidney The Origin of the Renal Artery Directly from the Aorta.

This kidney is from a case of monoxide poisoning The artery has been injected with lipiodol and the kidney x-rayed With a fairly direct route the blood reaches the glomerulus without many major divisions The branches of the main renal artery are the anterior and posterior branchings from which arise a number of interlobar branches These pursue a course which, toward their termination, is sometimes arched The interlobular arteries originate from the arched course and these give off the branches to the glomeruli With this magnification the glomeruli cannot be seen This arterial system is the structural framework upon which the nephrons are hung



Figure 14

Venous Drainage of the Kidney

This kidney has been injected by the main vein with lipoidal three days after death. The venous drainage of the kidney is extremely rich as seen in the accompanying x-ray. The branches are named much as the arterial branches. There is an additional direct drainage of the sub capsular venous sinusus to the hilum of the kidney by way of the interlobar veins.

The richness of the arterial supply and venous drainage of the kidney assures a rich circulation of this organ. The suggestion has been made that somewhere between 10 and 20 per cent of the blood circulating at one time is in the two kidneys. Most of the blood would appear to be in the veins rather than the arteries. The shunt by which the blood reaches the veins from the arteries without traversing the cortex is described on page 42.

which supports the endothelium *of the vessel The smooth* muscle cells are separated by a carbohydrate containing amorphous material both from one another and from the elastica In this arteriolar ground sub *stance the reticulin* fibers terminate after coursing between the tubules The arterioles are thus firmly bound to the tubules and glomeruli since the reticulin fibers terminate also in relation to the basement membrane of these structures

In the portion of the afferent arteriole nearest the glomerulus the smooth muscle cells loose their fibrils and may contain granules in their cytoplasm This appears to be the normal condition in some animals but whether or not these same granular afibrillar cells exist in the normal human can be argued *The efferent arteriole is somewhat larger in caliber* than the afferent but its muscular cells are not nearly so well developed It may be difficult to recognize smooth muscle cells in the efferent arteriole *in such conditions as heart failure in which the vessel is dilated*

The veins of the kidney are remarkable in at least two respects In the first place they are extraordinarily large (Fig 14) or extremely dilatable Secondly they possess an intimal longitudinal muscle bundle resembling the veins of the corpus cavernosum Valves can be made out in the veins especially at the corticomedullary level and in the interlobar veins (It is customary to use the same names for the veins as for the arteries *i e* renal interlobar arcuate interlobular veins etc)

THE NERVES OF THE HUMAN KIDNEY

This subject can be dismissed in short order Nothing definite is known about the nerve supply of the functioning portion glomerulus and tubule There is some comparative evidence to suggest a rich nerve supply Nerves can be followed in as far as the larger *vessels but actual demonstration of* nerve fibers in the higher mammals and man is extraordinarily difficult technically

Stimulation of the splanchnics in various animals and man alters *the color* of the kidney suggesting nervous control of circulation Times of stress appear to alter the volume of urine produced The exact anatomic basis for this is not yet demonstrated

Demuylder has described[2] nerve terminations at the glomerular root and in the macula densa in embryos (*cf* p 38) The confirmation of these findings in the same distribution in the adult kidney might be sig nificant

THE GLOMERULAR ROOT

It will be recalled that the distal tubule regularly returns to its glomeru lus of origin nestling in the angle between *the afferent and the efferent* arteriole (Fig 15) This area comprising the juxta glomerular portion of the arterioles the glomerular root and a segment of the distal tubule

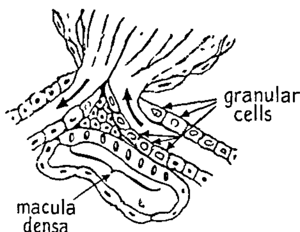


Figure 15

Relationships at the Glomerular Root

This diagram is intended to show the distal tubule attaching itself into the angle between the afferent and efferent arterioles There are modifications in the structure of the arterioles and of the distal tubule Granules occur in the cells of the arterioles in some conditions (*cf* p 38) The distal tubule has an arrangement of nuclei to form the macula densa These cells are more columnar than the others at this level of the tubule (*Courtesy of the Lancet from McManus J F A The Juxtaglomerular Complex, October 3 1942*)

shows peculiarities of structure in each of these elements The whole is moreover bound together by reticulin (Fig 16) in such a fashion that in conditions separating the tubules from one another *e g* leukemia the relationship between glomerular root and tubule is still maintained There is then not even a potential space between the cells of the distal tubule and those of the glomerular root

The cells of the distal tubule adjoining the arterioles tend to aggregate and become columnar as Zimmerman pointed out in terming these cells the "Macula Densa"[114] The cells of the macula densa show a reversal of their Golgi element, *i e* the Golgi lies on the attached side of the cell rather than on the lumen side of the nucleus as it does in other parts of the distal tubule (Fig 17) In certain species these cells of the macula lack lipoid mitochondria[75 76]

The juxta glomerular portion of the afferent arteriole frequently has the usual smooth muscle cells replaced by cells lacking fibrils and containing granules in the following conditions—crush kidney malignant hyper tension cirrhosis of the liver and Addison s disease[83] It is not customary to find these cells in their granular form in normal kidneys nor in essential hypertension in chronic glomerulonephritis or pyelonephritis[80] The suggestion that these granules represent the site of renin formation[82] ap pears not proven

The cells of the glomerular root are usually granular when the arteriolar cells are granular and resemble arteriolar cells under various conditions *i e* they possess a folded nucleus a prominent centrosome and are larger than the usual muscle or connective tissue cell A suggestion that some of these cells are nervous in origin has not be substantiated or repeated

Oberling in his first description of the juxta glomerular afibrillar cells in man compared them to the cells of the glomus body[83] He suggested a similar role of vaso regulation for these cells on the glomerular circulation Goormaghtigh after Zimmerman s description of the macula densa postu lated the macula densa in the distal tubule as the affector area[43] The proposition of the fluid in the distal tubule regulating the vascular pres sures within the glomerulus by acting upon the arteriolar cells is suggested chiefly by the reticulin pattern at the glomerular root and by the reversal of the Golgi element in the cells of the macula densa

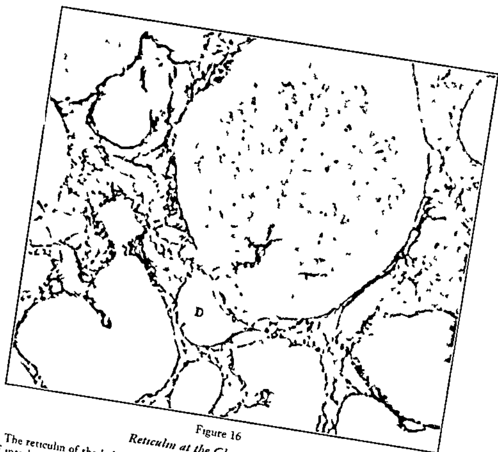


Figure 16

Reticulin at the Glomerular Root

The reticulin of the kidney is shown with selective silver stains It is seen as a collection of interlacing fibrils which terminate in one extremity on the basement membrane of the tubules and on the other extremity on the vessels There is no reticulin in the glomerulus Some fibrils can be made out in the section about the tubules The distal tubule (*D*) immediately beneath the glomerulus is not completely separated from the arteriole as one tubule is separated from another in the rest of the kidney This deficiency in reticulin is a constant feature of the glomerular root It is most obvious in lower animals and in infancy

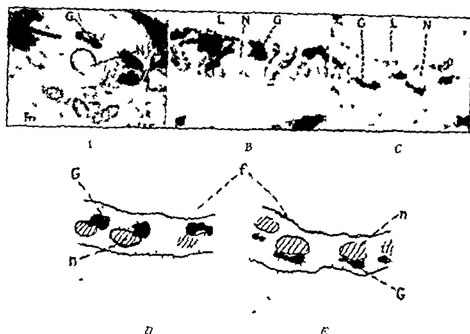


Figure 17

DaFano Impregnation Renal Tubular Cells

The illustrations above show the position of the Golgi element in the cells of the distal

attached side of the nucleus

This would suggest that at the macula densa some material is reabsorbed from the contents of the tubule lumen into the blood stream The preparation is from a cat kidney but the same features can be seen in the human (*Courtesy of the Quarterly Journal of Microscopical Science*)

Part II. The Diseased Kidney

Chapter 3

GENERAL REACTIONS OF THE KIDNEY TO INJURY

THERE is no essential difference in the agents which produce renal disease from those which produce disease anywhere else in the body. Inflammatory lesions and vascular derangments make up the bulk of the disease conditions to be discussed in this monograph.

Inflammation in the kidney is marked by hyperemia, exudation, emigration of white cells and the diapedesis of the red cells in the acute stage. In the chronic stage lymphocytic, macrophage, and fibroblastic activity predominate as in chronic inflammation elsewhere. But these protean reactions are modified by the structure of the kidney much as inflammation in the lung is influenced by structure to produce a pneumonia, or in the meninges to produce meningitis. The degree of functional impairment will vary with the diffusement of involvement. The same factor determines the permanent damage.

ADJUSTMENTS OF THE RENAL CIRCULATION

The kidney has been considered in the present presentation as a group of homogeneous units—the nephrons. The first point of reference of the newer views on the renal circulation is the recollection that the group is *not* homogeneous except in consisting of the same number of parts in the same order.[103] A nephron in the outer part of the cortex appears to have a short loop of Henle, while the nephron in the inner part of the cortex possesses a long loop of Henle.

Intermediate varieties are found, as expected, in the middle portion of the cortex. Peter had described these differences long ago.[87]

The difference between the nephrons consists further in diversity of the distribution of efferent glomerular vessels. The nephron in the outer part of the cortex has an efferent arteriole from the glomerulus which breaks up into a capillary plexus arborizing about the tubules in the classical description. As opposed to this capillary termination, the efferent arteriole of the glomerulus in the inner, or juxta medullary, portion of the cortex terminates in relatively broad venous channels which drain in precipitous fashion into the venous pathways of the organ.

The Oxford workers have shown in a variety of experimental animals and in man that under conditions of reduced renal arterial flow the circulation through the kidney becomes predominantly medullary and inner

cortical This may be due to the easy vascular channel provided by the efferent arterioles of the inner cortical nephrons draining directly into the venous channels[103] In states of reduced pressure the blood takes the course of least resistance In normal conditions the blood flow travels in the cortex without preference in the abnormal conditions associated with reduced renal blood flow there is a predominantly *medullary route* The *renal circulation in shock* appears to follow the course which Trueta has described Lauson and others have shown that the normal renal blood flow which may amount to 20 per cent of the total circulating volume *may be reduced to 1 or 2 per cent of the total in shock*[56] A part of the circulatory adjustments in shock which appear to conserve blood for the cerebro pulmonary cardiac circulation *may leave the kidney in a state of relative* or absolute ischemia It can be shown with the histochemical method for alkaline phosphatase that in prolonged shock *there is loss of alkaline* phosphatase in all but the juxta medullary portion of the cortex (Fig 18) Grossly in shock states there appears to be reduction in the blood flow to the outer cortex It is interesting to note that Hayman and Starr in 1925 observed the emptiness of the superficial glomeruli in the rabbit cortex during hemorrhage although the inner cortical glomeruli were full[50]

Bilateral cortical necrosis of the kidneys compares in most respects to necrosis of all but the juxta medullary portion of the cortex as the Oxford workers point out The condition is characterized by anuria of sudden onset It is frequently associated with pregnancy and convalescence from exanthemata but may be seen in a variety of chemical poisons The necrosis is usually conglomerate in fact involving both kidneys After severe wounding we have seen both kidneys peppered with infarcts of a rectangular portion of the cortex *sparing the corresponding juxta medullary cortex*

The crush kidney or the kidney after severe wounding was recognized in World War II *as a peculiar type of renal failure* which followed injuries of various parts of the body especially the muscles Clinically after recovery *from severe shock* the patient would appear to be progressing satisfactorily but would die in uremia a week or so after the injury Oliguria or anuria marked the clinical course but a terminal polyuria was seen not infrequently The elevation of the blood urea was progressive

The kidneys at autopsy were heavy and swollen the cut surface bulged past the capsule The cut surface showed congestion except for a paleness of the juxta medullary zone Brown streaks could be seen in the cortex or medulla or both following the lines of the tubules Microscopically the glomeruli themselves were normal but the capsule was dilated Bowman s space frequently contained granular albuminous *material* The parietal epithelium of Bowman s capsule was cuboidal The epithelium of the tubules was generally *flattened* Casts of hyalin variety with hemoglobin and cellular casts were numerous A striking feature was the so called tubulovenous thrombosis (Figs 19 and 28) in which a hyaline cast penetrated through a defect in the wall of the tubule and into a vein or



Figure 18

Alkaline Phosphatase Shock and the Crush Kidney (Whole Sections)

The middle three sections are of kidney from a patient who was in shock for three days before death The gross kidney is shown in figure 49 The upper and lower sets are from crush lesions In the shock kidney there is a loss of the enzyme in the outer part of the cortex (*cf* p 42) In the crush kidneys there is a patchy absence and a generalized decrease of the enzyme (*Courtesy of Bulletin of International Association of Medical Museum*)



Figure 19

Tubulo venous Thrombosis

This photomicrograph shows the fashion in which the venous thrombi are produced. There *is a rupture of a hyaline cast through a thin wall of the vein. The thrombus is laid down* on top of this.

In the present illustration the curling of the thrombus suggests that maybe the cast itself is forming the thrombus. There is a very slight inflammation seen in the interstitial tissues.

These tubulo-venous thromboses are seen after three days in the crush kidney. The crush lesion most reasonably is considered to be a failure of renal function depending upon the *prolonged* anoxemia of shock. Additional complicating factors may be vomiting or the excretion of blood degradation products.

venule with a thrombus attached to it The interstitial tissue appeared edematous and lymphocytes and plasma cells were seen frequently around veins The arteries generally showed no lesions but there was hyperplasia of the granular cells of the renal arterioles

Comparing this crush kidney to the shock kidney it will be appreciated that the pale inner zone of the cortex of the crush state (Fig 46) corresponds to the juxta medullary cortical zone of the shock kidney in which the circulation is best maintained (Fig 49) In phosphatase preparations the patchy loss of phosphatase of the outer portion of the cortex (Fig 18) contrasts to the well preserved juxta medullary portion It seems that some restoration of cortical phosphatase follows recovery from shock but the injured tubules are not able to handle any added effort such as is required by the excretion of hemoglobin (the transfusion kidney) myohemoglobin (the crush kidney) or acid base maladjustments as in severe vomiting etc

It is probable that most or all of the conditions in Lucke s lower nephron nephrosis (p 87) can be followed by renal failure of the crush variety They have in common a period of shock The lack of hemoglobin or myohemoglobin to excrete makes one wonder if some of the hemoglobin casts are not actually urochrome casts

The crush kidney has been stressed for several reasons Practically it is the most common variety of acute renal failure in which a pair of kidneys can pass within a week from absolute health to fatal insufficiency That is true in civilian life and it is the chief cause of death in cases of wounds which survive two days under wartime conditions Again the tubulo venous thrombosis and the hyperplasia of the granular cells of the renal arterioles serve as prototypes of similar reactions seen in a number of other conditions

THE GLOMERULUS INFLAMMATION

The subject of glomerular inflammation can be discussed from two view points as regards the acute stage (1) Distribution—focal lesions and diffuse lesions and (2) etiology—bacterial and the idiopathic or non bacterial lesions Some of these nonbacterial diffuse inflammatory lesions may be allergic in origin We are not familiar with any focal allergic inflammations of the kidney

Diffuse inflammation in the kidney of bacterial origin can be recognized as either ascending—derived from the pelvis and ureter—or as hematogenous—blood borne The hematogeneous type produced glomerular alterations chiefly by endothelial proliferation and by focal necroses Ascending infections early limit their appearance to the ducts of Bellini and the interstitial tissues of the pyramids The rapid involvement of the tissue spaces and the lymphatics disperses the infection throughout the kidney Sometimes one kidney is involved in the ascending diffuse in

flammation while the other is spared This unilateral disease is not usually seen in the hematogeneous inflammations

Focal necroses of the *glomerular capillaries are* seen especially in septicemia and bacterial endocarditis and are commonly marked by thrombosis of the adjacent capillaries of the tuft (*Figs 20 and 21*) *These incomplete* lesions of the glomerulus involving only a few capillaries are noteworthy in several respects (1) The majority of the capillaries *of the glomerulus* remain intact good evidence of the non anastomatic route of the capillaries and (2) the intercapillary space is not involved This latter feature separates the hematogeneous diffuse lesions whether or not associated with necrosis of portions of the tufts from the nonbacterial diffuse inflammatory lesions This latter may supervene on the bacterial type but the features to be described should allow the separation of the lesion

The non bacterial diffuse inflammatory lesions always bilateral are marked by several features (1) In the early stages involvement of the glomerular root by the inflammatory cells—particularly the macula densa (Fig 22) (2) Marked damage to the capillary walls producing hematuria and albuminuria (3) Acute inflammation in the intercapillary space These features will be discussed in detail

The glomerular root is one of the best locations to recognize this type of lesion Early in the inflammation damage to the macula densa can be *recognized by loosening of the cells and pyknosis of their nuclei with* polymorphonuclear leucocytes replacing the macula densa (Fig 22) This period of *acute inflammation* in the macula appears briefly but the polymorphonuclear leucocytes present in the afferent arteriole at the same time persist longer

The early involvement of the glomerular capillaries is seen as margination of leucocytes The endothelial cells swell and appear to multiply and the space of Bowman s capsule can be seen to contain erythrocytes and coagulated protein The red cells and protein appear in the kidney tubules as casts and in the urine as hematuria and albuminuria

The acute inflammation of the intercapillary space appears as a lobation of the glomerulus under low magnification (Fig 23) The basis for this is seen under suitable magnification and with the periodic acid Schiff s reagent coloring of the section It appears to be an *acute inflammation of* the intercapillary space with polymorphonuclears present in fair numbers I can find no *histologic basis for the suggestion* that this involvement of the central portion of the loop system is due to matting together of the *adjacent capillaries*

The later progression of these glomerular lesions is marked by several features The capillaries of the glomerulus show thickening of their walls this is an uncommon single termination of the acute process It is seen as a rule in association with proliferation of the epithelium of Bowman s capsule upon the framework of coagulated strands of fibrin in the capsular space

The further proliferation of the capsule epithelium forms a disc like



Figure 20

Embolized Glomerulus, Subacute Bacterial Endocarditis Adult

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of the [illegible]

Enough glomeruli may be embolized to produce renal failure when the course of subacute bacterial endocarditis is long. This eventuality is rare. A true acute glomerulonephritis sometimes supervenes. The embolization of glomeruli produces hematuria and albuminuria. The condition is differentiated from acute renal failure, including acute glomerulonephritis, by the normal blood chemistry, even in the absence of the cardiac lesion being recognized.



Figure 21

Embolized Glomerulus, Bacterial Endocarditis, Child

This peculiar lesion is seen in the kidneys during bacterial endocarditis in children It consists of a hemorrhage which fills most of the capsular space, compressing the glomerulus The erythrocytes are packed together with little fibrin The mass is covered by epithelium and connected to the glomerulus The origin of the erythrocyte mass, whether within a capillary loop or by a hemorrhage into the capsular space, cannot be decided

These lesions have been long described and illustrated by many authors

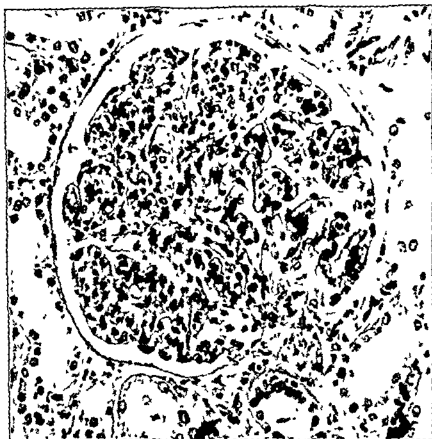


Figure 22

Acute Glomerulonephritis Hematoxylin Eosin

This glomerulus is from a case of acute glomerulonephritis dying in the sixth day of illness The polymorphonuclear cells are numerous in the glomerulus At many points the leucocytes lie next to basement membrane of capillary loops This recalls the margination of leucocytes seen in acute inflammation elsewhere

The polymorphonuclear leucocytes in the macula densa are characteristic of the disease in its early stages The same lesion is shown in figure 40



Figure 23

Acute Glomerulonephritis Glomerulus

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... y normal The
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illustrations of acute glomerulonephritis

mass of epithelial cells which appear crescentric in sections These are the epithelial crescents about which so much has been written The resemblance of the crescents to ramifying connecting sets of tubules has been stressed by MacCallum It is seen especially well in preparations with the periodic acid routine (Fig 42) This pseudotubular arrangement in the crescent appears at times to destroy the original basement membrane of the parietal layer of Bowman s capsule

Obsolescence or progressive disappearance of the glomerulus following acute diffuse nonbacterial inflammation of the kidney proceeds by scarring and fibrosis This extends from the intercapillary space and encroaches upon the lumen of the capillaries This is an important element and equal to or more important than the crescent formation and capillary wall thickening It seems likely that no single one of these features can exist without the others but their relative importance may vary from case to case

So much for the obviously inflammatory lesions of the glomerulus in their acute stages A few other lesions can be recognized in the intercapillary space with sufficient clarity to consider them as metabolic disorder rather than as inflammations The first of these is seen diffusely in eclampsia in a few glomeruli in some other diseases and takes the form of a reticulation or vacuolation of the intercapillary space The second is the deposit of a carbohydrate containing protein in the intercapillary space in the intercapillary glomerulosclerosis of Kimmelstiel and Wilson Finally some cases of lipoid nephrosis in children will show an accumulation of triglyceride fat in the intercapillary space

THE TUBULES

The tubules show a variety of particular lesions which are usually described as degenerations—fatty degeneration hyaline or colloid droplet degeneration hydropic degeneration etc The term degeneration is unsuitable in most respects but it usually is taken to mean an alteration not necessarily terminating in the death of the cell These particular changes are best considered as disorders of metabolism but the fashion in which they occur is not always obvious

The collection of colloid or hyaline droplets 1 to 2 μ in diameter in the epithelium of the proximal convoluted tubules appears related to protein in the tubular contents (Fig 24) It is compared to athrocytosis the process by which some lower animals with open nephrons recover the protein in the tubular fluid which has been derived from the cœlomic fluid [60] The hyaline droplets are high in carbohydrate but lack phosphatase They replace mitochondria in the segment of the tubule in which they occur There is usually an associated thickening of the overlying basement membrane

Fatty changes in the tubular epithelium is usually confined to the proxi

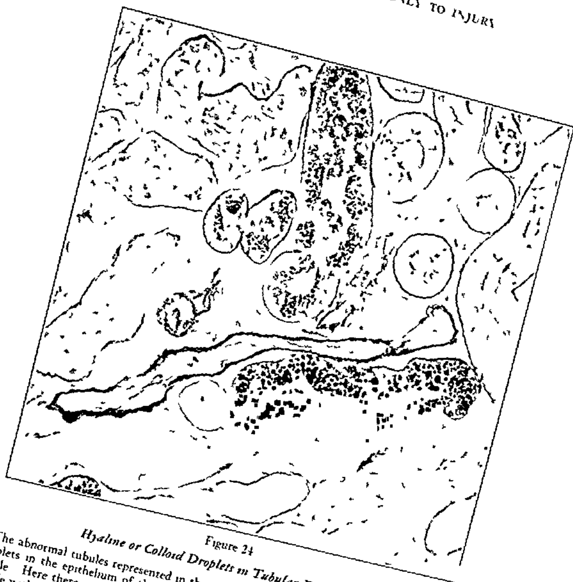


Figure 24

Hyaline or Colloid Droplets in Tubular Epithelium

The abnormal tubules represented in the photomicrograph above show hyaline or colloid droplets in the epithelium of the cells The greater concentration is shown in the lower tubule Here there is thickening of the basement membrane of the tubule An atrophied tubule with a much thickened basement membrane is running across the center of the field from left to right

The presence of colloid droplets was formerly understood to represent a serious degenerative change The newer information would suggest that the colloid droplets in the tubular epithelium represent reabsorbed protein The process is somewhat similar to athrocytosis in the lower animals (*cf* p 51) (*McManus, courtesy of Amer Jour Pathology*)

al convoluted tubules The relation to the mitochondria is not certain i the liver the accumulation of triglyceride fat is related to disordered hospholipid metabolism The kidney mitochondria like the liver mito iondria are composed of phospholipid in part It would seem that the tty change in the kidney tubules represents a failure of phosphate inding to the triglyceride and or the choline or ethanolamine com ination (See Reference 100) The appearance of triglyceride fat then ppears to be a disorder of metabolism in the cells of the proximal con oluted tubules It should be recalled however that fat accumulation f extreme degree occurs normally without apparent functional dis rder in the cat and dog

Vacuolation of the tubular epithelium of severe degree is sometimes alled hydropic degeneration This is seen especially when sucrose olution has been given intravenously in cases of cerebral disease An ther degenerative change of less appreciable degree is the so called cloudy swelling This appears in sections as swollen epithelial cells with ranular cytoplasm and poorly defined irregular lumen surfaces The hanges of autolysis and of cloudy swelling merge so closely that they are idistinguishable I have not seen cloudy swelling in biopsy material

Necrosis of the tubular epithelium shows the features of necrosis else here—pyknosis karyolysis and karyrrhexis of nuclei hyalinization and cidophilia of the cytoplasm The tubular cells show a tendency to be ome detached from the basement membrane They may be cast off and ie free in the tubular space Older necrotic cells which are not cast off may become calcified (Calcification of tubular epithelium without necrosis nay be seen in cases in which calcium is being excreted in excess)

Following necrosis of the tubular epithelium there may be regeneration f epithelium from surviving cells Mitosis may be seen in these instances und the regenerated cells are flattened and basophilic The exact cyto ogic features of the mitochondria and Golgi element in regenerated ells has not been described Their basophilia seems due to accumulation of ribonucleic acid in their cytoplasm

Pigmentation of tubular epithelial cells is not frequent The proximal onvoluted tubules appear to resorb hemoglobin in hemoglobinuria but it is only in conditions such as sickle cell anemia that the necessary degree of iemoglobinuria lasts long enough to produce ferrous iron in the epithelial ells In adults the pigmentation may appear as yellow granules in the pithelial cells In infants the iron content is not obvious but can be shown with the Prussian Blue reaction

In transfusion kidneys and in the crush syndrome fine yellow granules appear in the juxta nuclear zone of the epithelium of the distal ubules These granules do not color with the Prussian Blue reaction They may be hemoglobin or urochrome A pigment of similar character may be seen in the proximal convoluted tubule cells in some cases of amyl oidosis

Casts and exudate in the tubules are derived from the glomerular filtrate or exudate from ascending infection or from infection of the tubule extending from the interstitial tissues Casts of glomerular origin may contain many red cells and hyaline materials of protein type Cellular casts usually originate from tubular epithelium or from inflammatory foci

Before leaving the lesions of the nephrons one should mention the completeness of restoration which is possible *in acutely inflamed glomeruli* Some cases dying in the lipoid nephrotic stage of nephritis following an acute attack but dying of complicating infection rather than renal insufficiency may show a few glomeruli with crescents but most of the glomeruli are normal

The lesions of the glomeruli in vascular disease of the kidney will be described with the vessels Those of pyelonephritis will be described with the inflammations of the interstitial tissue

Finally *the ultimate fate of the tubule corresponding to the glomerulus* affected by a diffuse nonbacterial lesion which progresses may be in the direction of atrophy or hypertrophy The studies of Oliver have stressed this [65] In the tubule which atrophies as its glomerulus becomes obsolescent there is a thickening and frequently a duplication of the basement membrane which becomes wrinkled (Fig 24) The tubular cells fall together and accumulate pigment possibly a urochrome This atrophy may be throughout the length of the nephron or rarely restricted to a segment

The hypertrophied tubule on the other hand dilates and its cells become enlarged The basement membrane is stretched and may be thickened or thinned out The glomerulus may be recognized as a hyaline knot or may disappear completely A kidney which has been the seat of a progressive inflammatory lesion of the glomeruli may show atrophied as well as hypertrophied units The diseased kidney is made up of dissimilar units differing in functional capacity as opposed to the homogeneous nephrons of the normal organ

THE INTERSTITIAL SPACE AND STROMA

An edema of the interstitial space appears *in most acute inflammations* of the kidney and may be local or diffuse according to the nature of the underlying disease The collection of interstitial fluid in the crush or post hypotensive renal injury may be striking Interstitial fibrin may be stained in some of these conditions as well as following chemical poisoning of the tubular epithelium Fibrin interstitially would be expected to produce some scarring but such does not always seem to be the case Hemorrhage into the interstitial space is rare except in sudden heart failure purpura and *in purpuric phases of acute infections*

The inflammations of the interstitial spaces are the most interesting of the lesions of the stroma Pyelonephritis as this is called appears to be the most frequent single type of progressive renal disease It constantly

accompanies a pyelitis so that many of the cases are ascending However some cases of pyelonephritis are seen without lower urinary tract or renal pelvis infection and these are thought to be blood borne or descending The organisms involved are normally those of the coli aerogenes group but streptococci or staphylococci can be isolated from some cases

The usual acute pyelonephritis is seen in the so called pyelitis of childhood or of pregnancy There is a lesion of the interstitial tissue and ducts in a portion of the pyramid and this is followed quickly by radiating linear spread of the infection to the cortex If actual suppuration occurs in the subcapsular zone of the cortex the peri renal fat may be lifted up by the dissection of the infection A perirenal fibrosis may develop

Acute pyelonephritis may be unilateral or bilateral focal or diffuse The disappointing feature of the disease is that it tends to pass through periods of activity and quiescence one following the other until there is destruction of much of the kidney with replacement fibrosis Linear scars may be seen traversing the cortex and medulla The degree of scarring will depend upon the diffusement of the infection Vascular changes accompany the destruction of renal parenchyma Endarteritis obliterans of the type seen in the ovary and proliferative or hyperplastic arteriosclerosis predominates as Weiss and Parker have pointed out [11]

Weiss and Parker studied the natural history of pyelonephritis in many cases They recognize acute subacute and chronic stages with the microscopic picture characteristic of these stages of inflammation anywhere A healed chronic stage is described with thyroid like collections of tubules—a result of interstitial fibrosis—and the vascular changes mentioned above There may be little or no actual inflammation to suggest the pyelonephritic origin of the pathology

The process of obsolescence in the glomerulus follows a distinct pattern in acute and chronic pyelonephritis During the acute stage there is an acute inflammation surrounding the glomerulus—the periglomerulitis of Weiss and Parker This may occur without involvement of the glomerulus but usually a loop or so becomes adherent to the periglomerular inflammation is inflamed itself and further serves as a route along which the whole glomerulus may be involved and ultimately fibrosed The progression of this sort of lesion can be followed in figures 66 to 69

The destruction of segments of renal tissue becomes something in the way of arithmetical problem except for the fibrosis following pyelonephritis This extends further frequently than the obvious interstitial inflammation Associated with this is the vascular lesion sometimes out of proportion to the original damage as if the process got out of control

Pyelonephritic kidneys can be recognized grossly in a number of ways First of all the kidneys get smaller than in most of the other types of renal failure Secondly the size of the two kidneys may be different *i e* R 150 gms L 100 Thirdly evidence of previous or present lower urinary tract infection—cystitis ureteritis pyelitis—may be recognized

There is a variety of healed chronic pyelonephritis in which vascular lesions and hypertensive features clinically predominate The statistics of Bell make it evident that chronic pyelonephritis need not be associated with hypertension [9] When the disease is bilateral chronic and particularly healed hypertension appears to be the rule

This can be taken as an example of pyelonephritis being followed by a different type of disease Somewhat less obvious are the cases in which pyelonephritis follows glomerulonephritis or arteriolar nephrosclerosis A definite case in which classical glomerulonephritis terminated with the predominant pathologic picture of pyelonephritis has lately come to my attention I believe that some cases of glomerulonephritis have a complicating pyelonephritis aided or caused by distorted renal architecture and abnormal urine The pathologic picture may be completely taken over by the pyelonephritis lacking the criteria of glomerular disease such as were still present in the recent case I believe that the prevalence of the pathologic diagnosis of pyelonephritis and the scarcity of glomerulonephritis in anatomic diagnosis may be due to a secondary or supervening pyelonephritis The presence of foci of interstitial inflammation in the rare chronic glomerulonephritis may represent pyelonephritis in the course of development This feature is discussed at greater length on pages 120 to 121

ALTERATIONS IN THE VESSELS—ARTERIOSCLEROSIS AND AGING

The changes in the vessels which are described in diseased kidneys are practically restricted to the arterial circulation The veins and the capillaries have been studied very little and only recently in the crush lesion has any emphasis been placed upon venous lesions The arteries are the more conspicuous vessels Lesions in them are frequently associated with changes in their elastica allowing them to be demonstrated easily with special stains

There is however one frequently overlooked consideration in the interpretation of arterial hypertrophy a commonly described alteration In this condition the individual muscle cells of the artery appear large The course of the vessel is tortuous The lumen appears to be cut at different angles along a traceable course This appearance is seen most commonly in shrunken kidneys It may be that the loss of parenchyma has produced a redundancy of the vessel contributing to or responsible for the apparent hypertrophy The term hypertrophy or medial hypertrophy of the arteries should be restricted perhaps to kidneys of normal size

Reference has already been made to obliterative arteritis seen in pyelonephritis and in other diseases associated with destruction of parenchyma The same arterial change is seen in the ovary and uterus and in the lung with tuberculosis or other diseases with destruction of functioning tissue

These various situations of the lesion give us a clue as to the nature of the process concerned In each instance the decrease in the parenchyma supplied leads to the swelling of the intima and its thickening so that the residual lumen is of suitable caliber to carry the blood required by the residual tissue It is as if a street leading into a suburb became narrower with a decrease in population In obliterative endarteritis the narrowing is produced by the proliferation of intimal mesenchyma without elastic fibers and with little fat or hyaline deposit

Intimal elastosis of the arteries or duplication of the elastica can be considered as a definitely pathologic process The intima is increased due to the presence of two or more layers of elastica in place of the normal single layer of the intima (Fig 25) These elastica fibers are frequently eosinophilic after formalin fixation Elastosis of the intima of the smaller arteries is associated with hypertension but the nature of the relationship is not obvious

Fibrosis of the intima of the smaller arteries or prearterioles consists of the deposit of new collagen fibers in a concentric or onion peel fashion in the intima This also is a pathologic appearance and is seen in the kidneys of malignant hypertension forming an integral portion of the pathologic picture (Fig 54)

Arteriosclerosis of the arteries of the kidneys differs in no essential respects from that seen elsewhere The changes are seen in aging and are important only when destruction of parenchyma by ischemia is the result (Figs 26 and 27) Diffuse periarteritis or polyarteritis nodosa affects the kidney in many cases (Fig 28) Occasionally it is restricted to the kidneys and may be associated with hypertension Hypertension appears also in the course of diffuse periarteritis nodosa when the involvement of renal vessels is of considerable degree

Arteriosclerosis of the kidney is seen in many cases of hypertension It does not appear related to the duration or the degree of the hypertension It consists of the collection of a hyaline glycoprotein in the media and intima of the arterioles Lipoid (triglyceride fat) may be found in the hyaline in cases of lipemia Round globules of glycoprotein one half or less the size of the nucleus may be found in arteriole cells in some cases of hypertension It may be that they are precursors of the extracellular hyaline On the other hand the hyaline material resembles so strongly the intercellular substance of the normal arteriole that its origin in situ is suggested

Necrosis of the arterioles is restricted practically to malignant hypertension The outline of the constituent cells is smudged out and the whole is infiltrated with a weakly PAS—positive material (Figs 50 to 52) The lumen is the site of hyaline thrombi Inflammatory cell reaction may be seen For some reason the glomerular arterioles most frequently are the site of necrosis in malignant hypertension Necrosis of the glomerulus results (Figs 51 and 52)



F gure 25

Elastic Tissue Normal and Essential Hypertension

These photom crographs sho s branches of the renal artery The elastic t ssue has been colored with acid orce n Tl e artery at the upper left is presumably normal having come from a case of crush syndrome follo ving a ar wound The vessel at the lower left is from the same level of the kidney—the interlobar—and photom crographed at the same magn ficat on It is from a case of essential hypertens on and shows marked dupl cation of the internal elast ca or elastos s

The smaller vessels at the right are nterlobular arter es from a case of essent al hyper tension The s gnificance of this elastica hyperplasia is d scussed on page 57



Figure 26

Two Glomeruli with Ischemic Changes

These two glomeruli show ischemic changes wrinkling and thickening of the capillary [illegible] membrane and duplication of the capsular basement membrane There is a [illegible] of the right glomerulus The [illegible] is part of the atrophic process

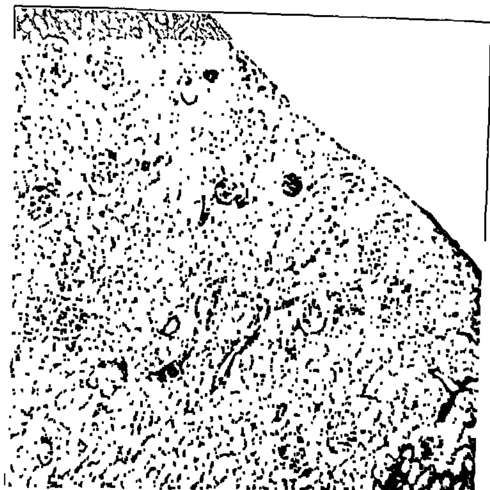


Figure 27

Subcapsular Scar, Arteriosclerosis

This low power photomicrograph shows a segment of cortex, immediately beneath the capsule A number of
spicuous by their thicke
at this magnification

This type of tissue loss is common in the kidneys of the elderly It does not cause recognized signs or symptoms The kidneys may be seriously pitted or scarred with arteriosclerotic infarctions A similar subcapsular lesion in healed pyelonephritis would show dilated tubules containing casts with a thyroid like appearance (*cf* Fig 70)

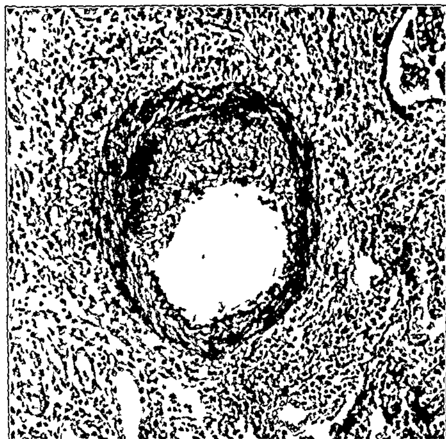


Figure 28

Necrotic Artery in Periarteritis Nodosa

The artery shows a necrosis of about half its wall. The structure is lost. There is infiltration with acute inflammatory cells. This extends also into the interstitial tissue. The internal elastica is recognizable for most of the circumference but is smudged out in its upper left area. There is a crescentic thickening of the intima in the involved upper half of the artery.

This lesion is sometimes part of the pathology of disseminated Lupus Erythematosus. The disease also called after Libman and Sacks who first described it, is characterized by atypical verrucous endocarditis, the skin lesion and renal involvement. One variety of glomerular lesion is shown in figure 98. Libman Sacks Disease is sometimes classed as a Collagen Disease. The term also includes Acute Rheumatic Fever, Dermatomyositis and Polyarteritis Nodosa. The validity of this concept is not established.

The veins are a neglected subject generally and especially so in the pathology of the kidney. Thromboses of the venules are relatively frequent and I have seen them in all types of disease of the kidney. Their significance is not certain. The striking tubulo venous thromboses of the crush lesion or post hypotensive states has been described. I am not sure that the lesion goes always from tubule to vein. In these conditions the venous pressure is raised and there may be some venous reflux into the tubule antecedent to the thrombosis. I have not seen an acute phlebitis in the kidney except in pyelonephritis and carbuncle. Chronic passive congestion of long standing produces a turgid purple cyanosed kidney which shows only dilated veins microscopically. Disease involving renal lymphatics is not recognized.

THE ISCHEMIC GLOMERULUS

A number of diseases which involve the arteries produce a similar or identical picture in the glomerulus. With this affect arteriosclerosis is the most important with peri arteritis, sarcoid, etc. seen also. It is probable that all these conditions produce a decrease in the blood supply of the portion of kidney supplied by the involved vessel. For this reason the glomerulus is called "ischemic" but this is not certain. The change affects primarily the basement membrane of the glomerulus. It was described by McGregor.[3] The lesion is well shown by the PAS technique and the following description is derived from materials so colored.

In its developed form the ischemic glomerulus looks somewhat shrunken. Earlier there is basement membrane wrinkling without thickening of a loop or more of the glomerulus. Later the basement membrane of glomerulus and capsule is thickened; that of the capsule may be split and duplicated (Figs 29 to 34). The glomerular tuft appears simplified, containing fewer channels than normal. I think that the glomerulus loses discreet intercapillary spaces and that the glomerular circulation becomes a pool with direct afferent efferent flow. In time the thickened basement membranes form a hyaline knot and the glomerular space becomes filled with a hyaline material of low carbohydrate content. There seems to be an endothelial lined channel left even in these knot like remains (Fig 34). This may be related to hypertension as Trueta et al have suggested.[16] The tubules atrophy and collapse with their typical basement membrane changes (p 54) when these glomerular changes are in progress.

Studying other, more normal appearing glomeruli, the earliest change appears to be a wrinkling of the basement membrane (Fig 29). This occurs before the thickening becomes apparent in the glomerular basement membrane and before any change can be recognized in the tubules.



Figure 29

Glomerular Wrinkling Essential Hypertension

[illegible]

This lesion is characteristic of glomerular ischemia from whatever cause (*McManus courtesy of Amer Jour Pathology*)



Figure 30

Wrinkled and Thickened Capillary Basement Membrane in Arteriosclerosis

This probably represents a somewhat later stage of the atrophy which is shown in figure 29. The glomerulus shows a thickening of the basement membrane of the capillaries usually after the wrinkling has begun.

One can sometimes make out portions of the glomerular basement membrane in which one area is wrinkled and thickened while another area is only wrinkled. I do not remember having seen a portion of the glomerular basement membrane in which there has been thickening without wrinkling in arteriosclerosis.



Figure 31

Arteriosclerotic Obsolescence

This represents a later stage in the obsolescence of the glomerulus from arteriosclerosis The basement membrane is very much more thickened and simplified There do not appear to be as many capillaries as usual There is considerable thickening of the basement membranes particularly of the capillaries The space of Bowman's capsule is filled in with a hyaline relatively acellular material



Figure 32

Arteriosclerotic Obsolescence

This represents another late stage in the disappearance of the glomerulus The vascular connection of the glomerulus can still be seen however There is beginning a disappearance of the parietal layer of Bowman s capsule



Figure 33

Arteriosclerotic Obsolescence

Th s llustrates another late stage n glon erular d sappearance There s more loss of the par etal basement of B wman s capsule There s a hyal ne arter ole sl own at a l ttle to the left of the center of the p cture at the top The tubular changes are taken to represent aut ly s s



Figure 34

Late Glomerular Obsolescence Arteriosclerosis.

This glomerulus was one in an arteriosclerotic scar The disappearance of the glomerulus appears nearly complete and the parietal basement membrane has quite disappeared With ordinary stain this would be seen simply as a hyaline knot in the microscopic section There is a persistent vascular channel through this glomerulus This channel may serve under certain conditions, as a by passing arterio-venous connection The relationship of the development of these short-circuiting connections to the development of hypertension has been suggested by Trueta but is not established (*cf* p 62)

AGING

It has been said well that arteriosclerosis is such an integral part of aging that the two are practically indistinguishable. Sometimes advanced age can be reached without much alteration in the vessels and in these instances the kidney appears entirely normal. One kidney from a male negro of one hundred fourteen years of age in my collection shows nothing abnormal apart from a very few hyaline thickened portions in the glomerular basement membrane.

Generally a few glomeruli or groups of glomeruli atrophy and show the ischemic change described. These are set in scars which contract to produce wedge shaped depressions in the capsular surface (Fig 27). The involvement of portions of vessels and the disappearance of a few glomeruli has been charted by Goormaghtigh for one case.[41] Oliver has reconstructions of many such kidneys and believes that a special sort of connective tissue scar may be found.[84] It is my impression that this is simply the result of a focal form of pyelonephritis not uncommon in the aged[45] (Fig 36). Cysts subcapsular in distribution may form in arteriosclerotic scars and reach a considerable size.



Figure 35

Atrophic Glomerulus with Giant Cells Renal and Generalized Sarcoidosis

Th

body type shown here



Figure 36

Alterative Glomerulitis, Hyaline in Arteriole and Tubular Atrophy

This illustration is from a kidney of an aged female dying with metabolic craniopathy Several lesions are shown The most conspicuous is the thickened basement membrane of the atrophying tubules This may be related to the glomerular fibrosis The arteriole shows several patches of subintimal hyaline There is interstitial inflammation This suggests that the lesion in the glomerulus is a pyelonephritis borne out also by the type of glomerular lesion (cf p 69)

Chapter 4

ACUTE RENAL FAILURE

THE three cardinal urinary signs of acute renal failure are oliguria proteinuria and hematuria There is considerable variation in the degree in which each is present in the individual case depending largely on the etiologic agent As a rule the patient showing purely acute renal failure does not have a change in the plasma proteins or a very marked anemia unless these are the results of an underlying disease Retention of the intermediate products of protein metabolism produces azotemia and acidosis There is frequently an edema which may be restricted to the lungs to the face to the dependant parts or it may be generalized

Hypertension of acute renal failure is restricted to moderate pressure elevations There may be an element of arterial spasm in those cases in which hypertension is present and marked In almost any case in which there is marked elevation of the blood pressure the termination of the disease rarely is caused by complete anuria from cortical necrosis or by a cerebral hemorrhage

The hematuria in most cases is the result of glomerular damage Extensive thrombosis in the renal veins can produce the signs and symptoms of acute renal failure The course is somewhat longer than the majority of the other types Hypertension was seen in one case of Bell s but one case at the Medical College of Alabama did not show any marked elevation of the blood pressure [9]

The proteinuria consists in large part of serum albumin There is some evidence that the serum protein is altered antigenically before it is excreted especially in acute glomerulonephritis [1,2] The preferential excretion of the albumin depends upon the fact that the molecular weight is less than that of the serum globumin Blackman seems to have demonstrated a relationship between the amount of fibronogen excreted in some cases of kidney injury and the amount of permanent damage [10]

The oliguria may vary in degree from a slight reduction in volume up to complete suppression of urine or anuria This feature may not be immediately apparent another indication of the usefulness of measurement of urinary volume in cases of renal damage Depending upon the capacity and irritability of the bladder the frequency of micturition may be satisfactory while the total volume approaches oliguria

Azotemia does not often reach the degree which is seen in the cases of chronic renal failure A sharp rise is often of more significance than the absolute level Severe symptoms may supervene when the azotemia is at a level which is tolerated with minor symptoms by the chronic renal invalid [88] In most instances the azotemia is derived from failure of excretion of the products of protein metabolism In some few cases the damage to

the kidney itself contributes to the level of the non protein nitrogen

In acute renal failure the edema may appear before the renal disease accompany it or appear later in its course A change in weight or a difficulty in tying ones shoes may lead to the patient or the physician noticing something wrong for the first time Some of the symptoms appear to be related to the edema of special parts of the body It has been suggested that the dyspnea is caused at least in part by the pulmonary edema The cerebral edema may contribute to the drowsiness coma and convulsions but it is the present opinion that retention of certain metabolites phenols and perhaps phosphates plays an important part [49] Frequently the edema fluid is high in protein a difference from the edema seen in the more chronic renal diseases

Acidosis appears to be the result of a failure to excrete organic acids in part The kidneys fail to produce the necessary base for the excretion of these materials and they accumulate in the blood In some cases of acute renal failure the acidosis may be a prominent feature In these instances the particular process responsible rather than the renal lesion appears to be the cause of the acidosis

The pathogenesis of the edema in renal disease is a subject of much discussion Capillary damage electrolyte balance and plasma protein deficit each contribute in various instances For a full discussion van Slyke s review [104] or a recent textbook of physiology should be consulted

Chapter 5

ACUTE GLOMERULONEPHRITIS

It has been recognized clearly at least since the time of Richard Bright (1827) that acute upper respiratory infections are followed in some instances by diminution in the volume of urine puffiness of the face and dark color of the urine [14] Bright described this combination of features in such a clear fashion that progessive renal disease especially those with an acute onset related to an upper respiratory infection has been known since as Bright s Disease He recognized that the material in the urine which coagulated on heating was albumen and the chronic disease of the kidney was associated with hypertrophy of the left ventricle now recognized as the result of the hypertension

The diseases caused by the streptococci—scarlatina and strep sore throat—were observed many years ago to be especially likely to be followed by acute glomerulonephritis or acute Bright s disease Since that time most of the other pathogenic cocci and in some few instances the gram negative rods have been shown to have a similar antedecent relationship The damage to the kidney appears while the infection is subsiding It has been suggested that the acute glomerulonephritis is an allergic injury to the kidney rather than the direct affect of the bacterial toxins [81] There is a disappearance of the circulating complement from the blood at the moment of the sudden appearance of the signs and symptoms of the renal injury [53] Both the loss of the complement and the explosive onset of the disease are taken to argue the participation of some sort of antibody—antigen system Something resembling human glomerulonephritis can be produced in the experimental animal by anti kidney sera [99] The disease is the dog is said to be more like the spontaneous disease in the human than it is in the rabbit or rat [38] There is no naturally occurring glomerulonephritis in animals

Acute glomerulonephritis is seen most frequently in children adolescents and young adults with no particular propensity for either sex Cases have been seen from infancy to old age but there is some suggestion that the acute disease in infancy may be a separate entity Streptococcal sore throat is probably the most common antecedent infection but streptococcal infections elsewhere especially in the skin and other infections may start off the chain of events [8] There is some evidence that the control of pyogenic infections is materially reducing the frequency of the disease

Clinically the disease is manifested as a decrease in urinary volume and a dark or smoky urine Edema occurs in the face and is sometimes generalized There are malaise and lassitude The urine is found to contain many red cells and much albumen It is usually of high specific gravity Generalized petechiae and pulmonary edema are sometimes seen and car

diac failure may occur. Hypertension can dominate the picture and cerebral symptoms may be severe. The diffuseness of organs involved has suggested to many that the kidney lesion is just one part of a widespread capillary disease.[8]

It has been pointed out in some series that the whole picture of acute glomerulonephritis does not appear in every case. Some cases will have the urinary findings alone with little systemic involvement. In others the cardiac manifestations are severe. It has been shown in one series that cardiac failure is frequent when searched for.[15] The degree of heart failure may contribute to the edema.[49]

GROSS PATHOLOGY

The kidneys are usually not enlarged but they may bulge past the capsule on cutting. They appear damp and show minute hemorrhages in the cortex. Sometimes the kidneys may appear quite normal grossly. Generally the gross appearance does not indicate the degree of injury to the kidney tissue.

The heart may be dilated. The tissues are wet and fluid is present in the serous spaces and subcutaneously.

MICROSCOPIC PATHOLOGY

The most striking alteration is seen in the glomeruli (Figs. 37 to 45). These appear relatively bloodless. There is a marked increase in the number of the endothelial cells of the capillaries of the tufts. This is responsible in large part for the cellular appearance of the tufts but a significant proportion of the cells in the glomeruli are polymorphonuclear leucocytes (Figs. 22 and 37). These line up along the capillary basement membrane much as they do in the margination of leucocytes in acute inflammation elsewhere. With suitable stains the intercapillary space of the glomerulus is prominent and contains polymorphonuclear leucocytes.[11] The glomerulus usually occupies all of Bowman's space and may protrude into the neck of the tubule.

The lumen of the tubule may be dilated slightly, contain red blood cells, granular and hyaline materials. Frequently hyaline droplets are in the tubular epithelium most often in the proximal convolution. The relative paucity of tubular alterations is responsible for the prefix glomerulo.

There may be acute inflammation of the afferent arterioles and, as has been mentioned, some of the polymorphonuclear leucocytes from the arteriole infiltrate the adjoining macula densa. Casts erode into the interstitial tissue and provoke an inflammatory reaction leading sometimes to thrombosis of venules (Fig. 45). This is not nearly so frequent as in the crush kidney. Edema of the interstitial tissue may occur to a severe degree and contribute to the swollen condition of the kidney.



F gu e 37

Acute Glomerulo iephritis Early Stage

The endothel al cells n the cap llar es of the glomerular tuf are extraord na ly numerous

The cap llary loop at the left about half way up the field sho v relat vely un n ol ed cap l lar es but the mesamg um s cons derably th ckened

The cond t on of a ute glomerulonephr s can be best ons de ed as the acute nflamma t on of the glomerular cap llar es and nte cap llary space

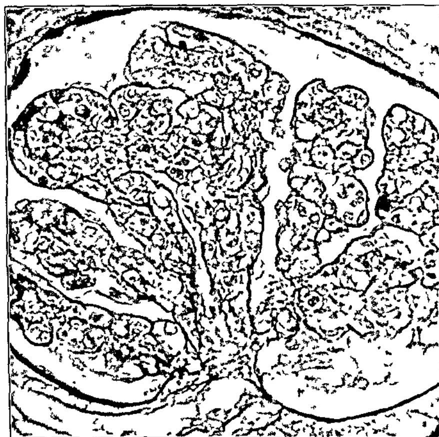


Figure 38

Acute Glomerulonephritis Cellular Features

This is a high power photomicrograph of a glomerulus in acute glomerulonephritis of six days duration The clubbing of the capillary loops is striking Many of the infiltrating cells are polymorphonuclear leucocytes Endothelial cell proliferation is marked No inter capillary space is recognizable The arteriole at the lower left is not remarkable



Figure 39

Acute Glomerulonephritis Necrotic Glomerulus

The glomerulus at the lower left shows the usual appearance of acute glomerulonephritis That at the upper right is made up of dilated capillary loops in which the blood cells are coalescent This latter glomerulus is called necrotic despite the lack of cellular reaction This type of glomerular change is an atypical but not unusual finding in acute glomerulonephritis

There is some thickening of a tubular basement membrane in the center of the picture



Figure 40

Acute Glomerulonephritis Polymorphonuclear Leucocytes in the Macula Densa

This is a case of acute glomerulonephritis of a few days duration The glomerular endothelial proliferation and cellular infiltration is characteristic Five deeply colored polymorphonuclear leucocytes are seen in the usual situation of the *macula densa* This lesion is characteristic of acute glomerulonephritis in its early stages It is seen also in figure 22



Figure 41

Acute Glomerulonephritis Two Weeks History

This is an early stage in the development of the characteristic crescent The capillaries of the tuft show the endothelial proliferation and acute inflammation The epithelial cells of the Bowman s capsule have proliferated to cover strands of fibrin which have been precipitated The fibrin is probably leaked through the damaged capillaries of the tuft



Figure 42

Glomerular Crescent Five Weeks

This illustration shows a later development of a crescent in glomerulonephritis The epithelial cells have further proliferated and are now beginning to arrange themselves into something resembling tubules, as in the upper part of the illustration The lower portions of the epithelium cells are more solid The further development of the crescent in subacute and chronic glomerulonephritis is shown in figures 77 to 81



Figure 43

Inter-and Intra-Capillary Lesions in Glomerulonephritis.

This is a glomerulus from a case of chronic or subacute glomerulonephritis The capillaries at the left are engorged and show proliferation of the endothelial cells with development of reticulin in relation to them The glomerular capillaries at the right show relatively normal loops but involvement of the intercapillary space

There has been discussion concerning the glomerular lesion of acute glomerulonephritis, whether it is inter or intra-capillary in situation As this picture shows it can be both



Figure 44

Glomerular Disappearance in Subacute and Chronic Glomerulonephritis, Lymphocyte Reaction

This glomerulus has been fibrosed. Some tubules, possibly remains of crescent formations (Figs. 42, 77 to 88), can be recognized at the left. The lymphocytes surrounding this glomerulus are much more numerous than is ordinarily seen. Some relationship to antibody production may exist in such lesions.



Figure 45

Interstitial Cast and Inflammation Acute Glomerulonephritis

The photomicrograph is from a case of acute glomerulo nephritis dying two days after on set. There is an interstitial cast that is a cast which has eroded through the tubule and into the interstitial tissue Some inflammation with lymphocytes surrounds this

The tubulo-venous thrombosis and the interstitial inflammation resulting from the rupture of casts from tubules has been brought into prominence by its frequency in the crush kid ney Actually the examination of a series of almost any type of acute renal failure shows that the interstitial casts and inflammation are frequent Tubulo venous thromboses are not un common

While the glomerulus appears to be involved in the early stages with an emphasis on the capillary endothelium in the later stages the most obvious alteration takes the form of proliferation of the epithelial cells of Bowman s capsule An increase in the number of cells of the capsule can be recognized within two to six days after the onset of the disease These grow into the space on a framework apparently derived from the coagulation of the protein leaking through the damaged capillaries (Fig 41) Within two weeks something resembling tubules can be seen in the proliferated epithelial cells of the crescent (Fig 42)

Further proliferation of the epithelial cells of the crescent may lead to an obliteration of these tubular structures (Fig 81) On the other hand the tubules may develop basement membranes of their own and persist past the stage of glomerular obliteration (Fig 80) The obsolescence of the glomeruli proceeds apace with the changes in the epithelium of Bowman s capsule The proliferated endothelial cells of the capillaries develop fibrils alongside them as MacGregor pointed out [76] Fibrosis occurs also as a rule in the intercapillary space Sometimes the fibrosis in the intercapillary space sometimes the fibrosis beside the endothelial cells is more striking These features have led some workers to speak of intra capillary or inter capillary lesions in the glomeruli in acute glomerulonephritis It is possible to see the two types of lesion in the one glomerulus (Fig 43) The distinction may well be arbitrary and artificial

Acute glomerulonephritis sometimes shows atypical histologic features These are always in addition to the endothelial proliferation and glomerular inflammation described Fairly frequently there is an acute arteritis sometimes restricted to the afferent arteriole and taking a necrotizing form [37] This may result in a necrosed glomerulus with hyaline material of granular appearance extending into the glomerulus from the arteriole In other instances necrotic glomeruli are recognized by the presence of dilated capillary loops distended with blood and lacking cellular proliferation and infiltration (Fig 39) In other glomeruli one can make out hyaline material in the capillary loops These are termed thrombi although no necrosis of the loops can be seen It is more probable that these are artefacts representing the coagulation of the concentrated plasma produced by some filtration Acute arteritis occurs occasionally in the interlobular and arcuate arteries

The structures in the kidney may show all the features of the basic infection upon which the acute glomerulonephritis is added For example in subacute bacterial endocarditis one may recognize embolized glomeruli in addition to the diffuse disease of the glomerulonephritis Frank abscesses may be seen in the kidneys when larger emboli or acute thromboses have resulted from the antecedent disease

The mechanism of production of the acute glomerulonephritis is not obvious from the study of sections of kidneys affected with the disease It has already been mentioned that the acute inflammation shows the signs

of the process elsewhere—margination of leucocytes, exudation of fluid, passage of red and white blood cells through the capillaries Bacteria have been searched for in the glomeruli affected but have not been found A personal observation of questionable significance is that in acute glomerulonephritis in the elderly the obsolescent and wrinkled glomeruli of arteriosclerosis (*cf* p 62) do not show the cellular proliferation and infiltration seen in the more normal glomeruli This may be due to the angiospastic nature of the disease which Volhard considers important[106] or it may be the result of the protective action of the material responsible for the thickening

Some mention should be made of Bell s "*Subclinical* ' *Glomerulonephritis*[9] This is marked by endothelial proliferation in the glomeruli without capillary obstruction The condition is not uncommon in severe infections as Bell points out The chief difference I can find between "sub clinical" glomerulonephritis and the actual acute glomerulonephritis is the absence of involvement of the intercapillary space This space appears normal in the subclinical glomerulonephritis, lacking the polymorphonuclears of the frank disease

Chapter 6

THE CRUSH KIDNEY

During the London blitz in 1940 pathologists observed peculiar lesions in the kidneys of those dying in renal failure after severe wounds, most often crushing injuries of muscle. Occasionally cases were seen in which there was only compression of muscle without any actual skin wound. Bywaters described these kidney lesions as being marked by the presence of hemoglobin casts in the distal tubules and in the collecting tubules.[17] The hemoglobin was presumably derived from the injured muscle and was identified in the urine by spectrographic methods. Shaw Dunn described the presence of tubulo venous thromboses.[28]

This lesion was considered a new sort of acute renal failure in 1940. A survey of the literature has shown that similar descriptions in Germany date as early as Pfeiffer's in 1897.[89] A study during World War I by Minami had described most of the important features but overlooked the tubulo venous thromboses.[7] There was no definite etiology suggested by Bywaters except the blockage by hemoglobin of the tubules or a toxic action of materials from the muscle directly upon the kidney tissue, the latter producing an unselective reabsorption.

The subject has been considerably enlarged by Lucké who says that a wide variety of injuries and diseases can produce a similar picture of acute renal failure.[63] The condition is called lower nephron nephrosis by Lucké. Included are any trauma to muscle, burns, transfusion with incompatible blood, wasting diseases of muscle, heat stroke, blackwater fever of malaria, toxemias of pregnancy, utero placental damage, alkalosis, sulfonamide intoxication and poisoning with certain vegetable and chemical agents.

The feature common to all the conditions described by Lucké appears to be an episode or period of shock of varying degree and duration. A certain number of conditions described by Lucké do have hemoglobinuria. The modern explanation of the crush syndrome and similar lesions in the kidney is derived, as previously mentioned, from the studies of Trueta and his colleagues.[100] It is though that during a period of shock there is an ischemia of the kidney. This leaves the kidney tubules unable to excrete without injury to such materials as hemoglobin and myo hemoglobin or unable to withstand such further insults as excessive acidosis or alkalosis.

In a survey of the first 1000 autopsies at the Medical College of Alabama 11 fatal cases of the crush lesion occurring in civilian life were found.[9] Three of these were accident cases. Mallory found an incidence of 18.6 per cent among 427 autopsies on battle casualties in the Mediterranean Theater.[67] Angevine and Harmon reported the renal lesion in 15.2 per cent of 1,065 cases.[8] It has been suggested that many cases of

chronic renal disease die in something corresponding to the crush condition This subject will be discussed later (p 112)

The clinical picture usually includes a recent period of shock Most frequently this is associated with injury wounding or an accident In some cases a severe hemorrhage of internal variety severe vomiting or or gastrointestinal upset appears sufficient to initiate the condition The period of shock may be extraordinarily brief In some cases it does not appear to have been recognized clinically This may suggest that renal vasoconstriction is not always attended by peripheral vasoconstriction

Shock when present is corrected as a rule without difficulty by whole blood and plasma transfusions The patient may appear to be doing well for a day or so or he may complain of a lack of urination If urinary out put is measured for the second or third twenty four hours after the accident or injury it will be noted that the volume does not exceed 500 to 1000 cc The urine passed is acid in reaction the specific gravity is low and tends to become fixed at 1 010 In some cases the urine may be blood tinged or dark in color for the first day or two This dark urine when present will give a positive benzidine reaction Spectrographic examination will show a heme pigment Pigment is excreted only during the first twenty four to forty eight hours as a rule Proteinuria is always present and persists throughout the course

The oliguria may terminate in anuria A return to normal volume or a polyuria may ensue The quality of the urine produced does not change very much The blood pressure tends to rise after the third day The NPN rises to extremely high levels The potassium and phosphate in the blood increase and there is a decrease in the alkali reserve Edema is not a constant feature and when present is seen usually in the lower ex tremities Pulmonary edema is seen and may cause the death of the pa tient in some instances The patient is drowsy but is not in coma and usually does no show convulsions Death usually occurs in seven to ten days Recovery does occur particularly when the urinary output is re established However I have seen death associated with a rising NPN and sing urinary volume past 2500 cc per day If oliguria and hyper sion persist an estimated 80 to 90 per cent die [67]

Gross Features —The kidneys are swollen They weigh from 200 to 250 ams each Unless there is previous disease the capsule strips with ease ne kidney tissue itself is soft The cut surface is wet The cortex bulges ist the capsule and there is a fine line of blanching just on the medullary de of the cortex (Fig 46)

The rest of the body does not show a great deal grossly There may be an excess of fluid in the different tissue spaces The heart is usually dilated and flabby The lungs may show edema The liver is swollen and may be fatty The evidences of the original injury or wounding when present need not be remarkable

Microscopic Appearances —In the kidney I think there are five distinct

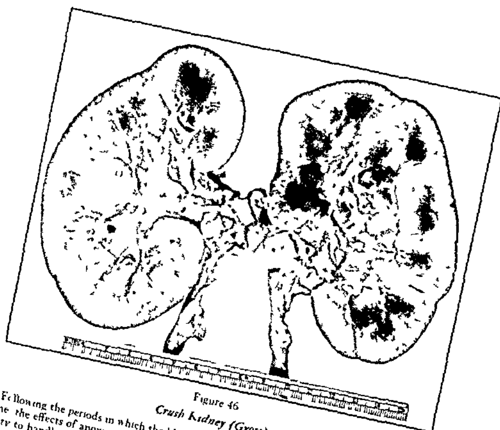


Figure 46

Crush Kidney (Gross)

Following the periods in which the blood pressure has been decreased seriously over a long time the effects of anoxemia are felt in the kidney. The chief deficiency is seen in the inability to handle and excrete hemoglobin from injured muscle or hemolyzed blood.

The kidneys are grossly somewhat swollen and weigh two hundred grams or so apiece. Their appearance is as shown in the accompanying picture. There is a blanching of the inner part of the cortex and some hyperemia of the medulla. The cortex bulges somewhat past the capsule.

features which can be seen with any fixation and stain They are (1) Normal glomeruli (2) Flattened tubular epithelium (3) Absence of colloid droplets in the epithelium of the proximal convoluted tubules (4) Casts in tubules including pigmented casts (5) Tubulo venous thrombosis There are in addition two other features which can be made out with adequate fixation and technique The first of these is the hyperplasia of the granular cells of the renal arterioles This is present whether or not there is hypertension The other feature is seen with the alkaline phosphatase method of Gomori[40] There is a diffuse loss of the quantity of alkaline phosphatase and a patchy absence from proximal convoluted tubules (Fig 18)

The glomeruli are normal inasmuch as there are no adhesions nor any obvious disease of the capillary loops (Fig 47) The space of Bowman may be dilated with cuboidal cells lining the parietal layer The space itself may contain granular material which is colorable with eosin

The tubular epithelium is flattened This is true of the proximal convolutions as well as the distal In a number of cases which I have studied personally there appears to be preservation of the brush border in the flattened epithelium of the proximal convolution There is usually no marked fatty change except in the distal convolution cells The cytoplasm may be granular in the flattened proximal convolution cells

The epithelium of the proximal convoluted tubules is remarkable in not showing any colloid droplets in the cells This is in the face of the constant proteinuria which these cases show during life It will be recalled that athrocytosis a process by which protein in the tubule lumen is recovered is a constant feature of normal epithelium in the presence of proteinuria (*cf* p 51) The absence of colloid droplets in the crush lesions suggests strongly that the epithelium is functionally not intact

There are casts in many levels of the tubules Greatest concentration is seen in the distal convoluted and collecting tubules In the proximal convoluted tubules the casts are granular With mitochondria preparations they can be shown to be derived from the epithelium of the proximal convoluted tubules (unpublished observations) Some red cells are seen and some polymorphonuclear leucocytes In the loops of Henle and in the distal convoluted tubules the casts show pigmentation and some of the casts in the distal tubules and further down are made up entirely of pigmented material presumably hemoglobin At times these casts both hyalin and pigmented erode into the interstitial tissue The interstitial tissue which is invaded by the casts shows an acute a chronic or a subacute inflammatory reaction with polymorphonuclear leucocytes lymphocytes and some eosinophiles There may be giant cell formation around these casts

The tubulo venous thrombosis is the result of the herniation of one of the casts through the interstitial tissue into a thin walled vein This

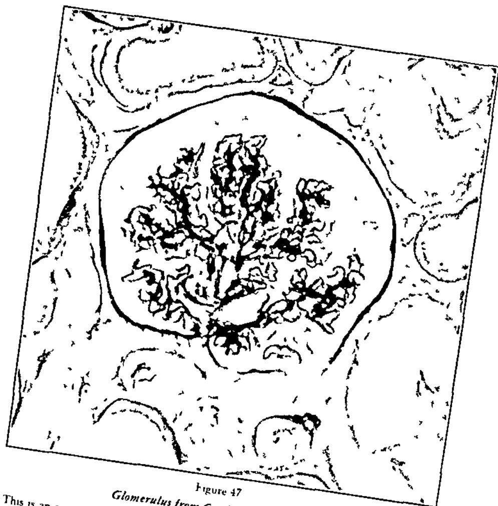


Figure 47

Glomerulus from Crush Kidney (PAS)

This is an essentially normal appearing glomerulus from a crush lesion. The glomerular capillaries may be slightly reduced in caliber but this may be the result of fixation. There is some granular debris in the glomerular space. It will be noted that some of the proximal convoluted tubules which can be identified by their brush border appear to contain granular material. Their epithelium is flattened with dilation of the lumen. (*McMan* ... courte y o *Amer J ur Path* / *g*)

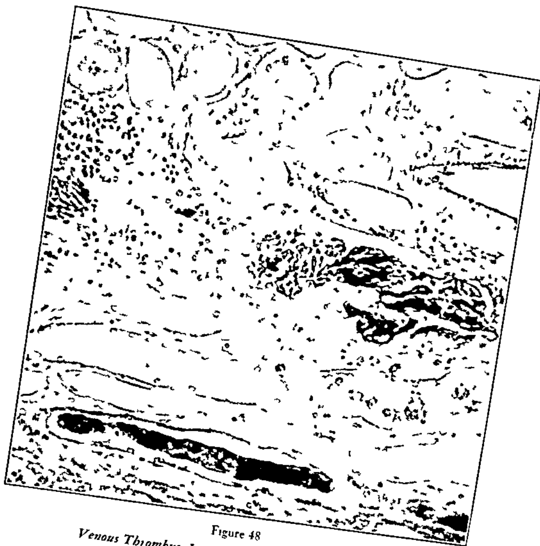


Figure 48

Venous Thrombus Interstitial Inflammation and Casts in the Crush Lesion (PASH)

This is a low power photomicrograph of a portion of a crush lesion There are granular casts above and hyalin casts below in this illustration The interstitial tissue shows inflammatory infiltration with lymphocytes a few eosinophiles and a very occasional polymorphonuclear leucocyte

The most striking feature of the illustration is the presence of thrombi in the vein The development of the thrombus in crush injuries is illustrated in figure 19

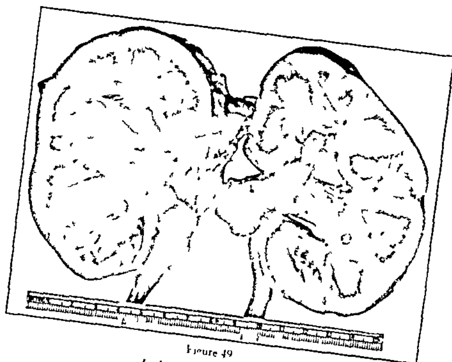


Figure 49

Kidneys in Shock (Gross)

It has been shown that there is a sparing of the circulation in the cortex during shock. The concentration of flow is in the inner or juxta medullary portion of the cortex. This appearance is well represented in the illustration above in which the whole kidney appears pale but there is some appearance of blood in the inner portion of the cortex. The kidneys are from a case of coronary occlusion with shock for three days before death. The phosphatase preparation of the kidney in the same case is shown in figure 18.

lesion is well shown in figures 19 and 48 These thromboses and tubular erosions are not usually seen until three days after the accident

The granular cells of the renal arteriole are probable most prominent in the crush kidney The granules are shown best with PAS There does not appear to be any relationship between the granules and the blood pressure It is unusual to see the granules until two or three days after wounding The tissue should be fixed in Zenker formol and dehydrated slowly for best demonstration of the granules

The reduction of alkaline phosphatase in the kidney generally and its patchy loss in some proximal convoluted tubules is an excellent indication of damage to the tubules The diffuseness of involvement and the fact that proximal tubules are involved is against the terminology lower nephron nephrosis

Chapter 7

ACUTE HYPERTENSION ECLAMPSIA

ACUTE HYPERTENSION

A CLINICAL variety of hypertension with a rapid course and death in kidney failure is sometimes termed Malignant Hypertension The term was introduced by Volhard to describe a form of hypertension and uremia occurring in young persons with a particular propensity for females [97] The concept of a special disease entity has had a history marked by disagreement among clinicians and among pathologists [9 38] Most authorities now consider the term a useful one suggesting that some cases of hypertension do run an acute course and die of renal failure It is though also that some cases of chronic hypertension may have a Malignant termination

In those cases which begin as acute hypertension and terminate fatally the blood pressure frequently passes values of 250 systolic and 200 diastolic Retinal hemorrhages are common Headache is distressing and episodes of amaurosis and hypertensive encephalopathy are characteristic Nausea and vomiting accompany the disease frequently forming one of the more unpleasant aspects of the disease Edema oliguria and hematuria are the most prominent signs of renal failure Albuminuria is constant and casts of hyaline and granular varieties are found Drowsiness coma and convulsions mark the terminal stage during which a condition approaching anuria may appear

Usually the kidneys are not much decreased in size There may be fine granularity of the capsular surface Petechial hemorrhages are present The line between cortex and medulla may be distinct or accentuated by congestion of the medulla Microscopically the vascular changes are most conspicuous The arterioles and smaller arteries have areas of necrosis with thrombosis sometimes suggesting the pouring of the necrotic material into the lumen of the vessel (Figs 50 to 53) The arteries of interlobar size show a marked thickening of the intima in a concentric laminated fashion This can be shown to consist of duplications of the intimal elastica (Fig 54) A similar change is found in some cases of Essential hypertension In effect this elastica hyperplasia changes the muscular artery into one of the elastic type as in the aorta where high pressure is usual

Glomerular changes of two main varieties can be seen The first and more frequent is the wrinkling and thickening of ischemia The other prominent glomerular lesion probably originates in necrosis of the afferent arteriole and is seen constantly with it This takes the form of a glomerulitis a proliferation of epithelium and endothelium which is not as diffuse as that seen in acute glomerulonephritis but otherwise resembles it con

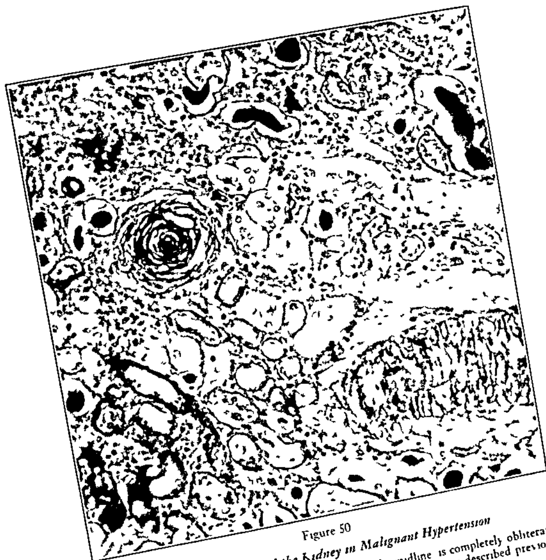


Figure 50

High Power View of the Kidney in Malignant Hypertension

An arteriole a little to the left of center and above the midline is completely obliterated This is a form of thrombosis and necrosis The tubules show changes described previously in this series

The arteriole entering the field from the lower right hand margin is cut in longitudinal section and shows the cellularity of the arteriolar wall There is marked interstitial inflammation

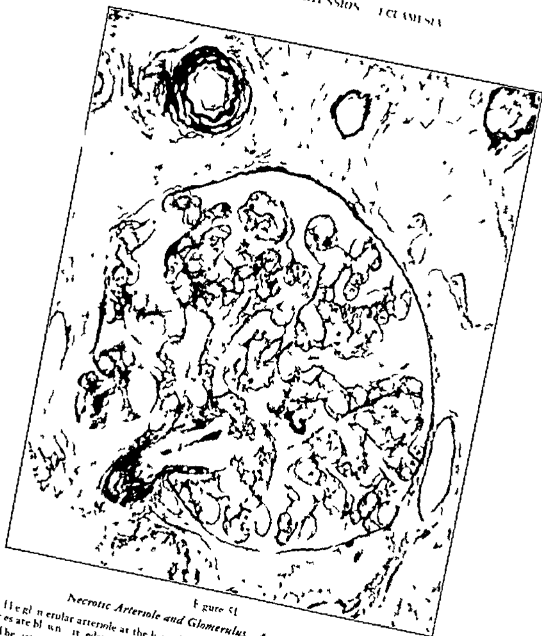


Figure 51

Necrotic Arteriole and Glomerulus. Acute Hypertension

The glomerular arteriole at the lower left is necrotic as is the glomerulus itself. The capillaries are blown up, edematous and are adherent to the capsule in places. The arteriole at the upper left shows an increased cellularity, the so-called hyperplastic arteriolosclerosis, and some hyalinization.

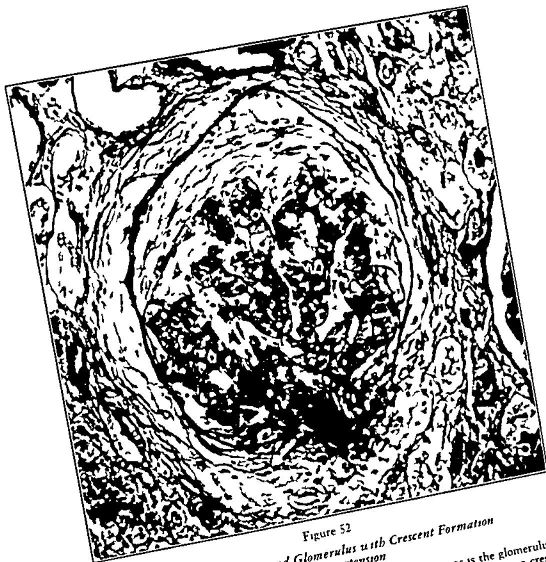


Figure 52

Necrotic Arteriole and Glomerulus with Crescent Formation
Acute Hypertension

The arteriole at the lower extremity of the glomerulus is necrotic as is the glomerulus i
self. The space of Bowman's capsule is filled with a fibrous structure resembling a cresce
but lacking any tubule formation. There is inflammation around the glomerular capsu
This type of change is unusual in acute hypertension.



Figure 53

Arteriolar Sclerosis and Necrosis Colloid Droplets in Tubular Epithelium Acute Hypertension

The arteriole at the upper left is necrotic. At the upper right arteriolar hyalinization is shown. The tubular atrophy and the increase of interstitial connective tissue are marked. The dilated tubule in the lower right has colloid droplets in its cells. This feature is discussed on page 103



Figure 54

Low Power View of Kidney in Malignant Hypertension

This is a low power view of a portion of the cortex in a kidney from a case of hypertension with rather an acute course The individual glomeruli show different stages of wrinkling an scarring The glomerulus a little to the left of the center and above is nearly completel obsolescent There are a number of atrophied tubular elements as shown by the thicken basement membranes

The small artery at the left shows very marked fibrosis of the intima Fibrosis of sm arteries is a striking feature of the disease (*cf* p 95)



Figure 55

Medium Power View of the Kidney in Malignant Hypertension

The arteriole a little to the left of center is markedly sclerotic. The glomerulus shown in the center of the field is apparently undergoing some type of necrosis. There are many tubules showing thickened basement membranes. Many other tubules are dilated and contain casts. There is a general increase in connective tissue.



Figure 56

Glomerular Root in Malignant Hypertension
Granular Cell Hyperplasia

The granular cells of the renal arteriole are shown here to be numerous *Similar findings* are seen in the "crush" kidney and in cirrhosis of the liver There is no definite relationship of the granular cells to hypertension as some workers have suggested (*cf* p 38)

siderably (Figs 51, 52 and 55) Adhesions form between the glomerulus and the capsule The proliferated epithelial cells of the visceral layer become filled with large colloid droplets Organization of the injured glomerulus may be seen but it is seldom that the course of the disease is long enough for this to be complete (Fig 52)

A tubular alteration is seen with regularity in acute hypertension but I do not find it described Dilated tubules are lined by enlarged cells full of colloid droplets (Fig 53) Groups of tubules are so affected perhaps all of one nephron It may be that this is associated with glomerulitis An injured glomerulus sometimes is surrounded by a group of dilated tubules with colloid droplets

The interstitial tissue in acute hypertension is usually increased in amount sometimes to such a degree that the relatively brief clinical course does not seem sufficient to account for the loss of parenchyma Chronic inflammatory cells chiefly lymphocytes are seen in these cases but seldom form sizeable collections Granular cells can be seen in the afferent arterioles and sometimes in the smaller arteries forming an intimal cushion They are best demonstrated with the PAS method on frozen sections of formalin fixed tissue (Fig 56)

ECLAMPSIA

One of the complications of pregnancy is the acute renal failure of eclampsia It is seen in the third trimester of pregnancy and may appear before or after the delivery of the child There is a 5 to 25 per cent maternal mortality and 20 to 40 per cent fetal mortality [26, 57, 98] The disease is usually ushered in by a period of abnormal weight gain The rate of weight gain is probably more important than the total weight gain as an indication of threatening eclampsia [25]

Eclampsia is regularly associated with an elevation of the systolic and diastolic pressures The rise in blood pressure may appear with the edema or precede it As in most instances of hypertension the diastolic blood pressure is a better guide to the progress of the disease than the more variable systolic pressure

The urine is reduced in quantity in most cases of eclampsia Oliguria may approach complete anuria Present with this there is a proteinuria frequently of severe degree The urine contains hyaline and granular casts red blood cells and white blood cells The hematuria is seldom as marked as in acute glomerulonephritis

Clinically there is headache nausea and vomiting drowsiness dizziness and tinnitus Convulsions of severe degree occur in nearly 100 per cent of the cases of eclampsia and many authorities would not make the diagnosis of eclampsia in the absence of convulsions A rise in the body temperature is taken to be a serious prognostic feature

The gross pathology of eclampsia is seen most frequently in the liver

next most frequently in the kidneys and less commonly in the other organs The liver lesions take the form of an acute necrosis which may be focal and sparse or so diffuse as to produce the featues of acute yellow atrophy The kidneys are usually slightly enlarged and damp but the most characteristic lesion is seen in the microscopic sections Necrotic foci may be seen in the spleen the brain and other organs

The constant lesion in the kidney in eclampsia is seen in the glomeruli [79] All that is noticed in the glomeruli in the ordinary hematoxylin eosin stain is a slight excess cellularity including the preservation of many of the visceral epithelial cells With the PAS method it can be seen that the capillary loops are discrete erectile and separate one from another (Figs 57 to 59) Associated with this and perhaps causing the appearance one can make out a fine reticulation and vacuolation of the inter capillary space This sometimes extends into the adjacent endothelial cells of the capillaries (Figs 60 61) The condition corresponds to an edema of the tuft [51] There is no thickening of the glomerular basement membrane contrary to the usual descriptions Glomerular edema may be both cause and effect of the generalized failure to excrete fluid and electrolytes Tubular changes include fatty change colloid droplets granular and hyaline casts and other nonspecific lesions

Bell makes the statement that the renal lesions are seen more consistently in eclampsia than the liver necroses [9] Shaw Dunn described reticulation of the tuft and illustrated it [8] Many of the current textbook illustrations actually show vacuolation of the tuft in eclampsia—*e g* Anderson s *Synopsis of Pathology*—while calling it something else usually thickening of the basement membrane [4]



Figure 57

Glomerulus in Eclampsia

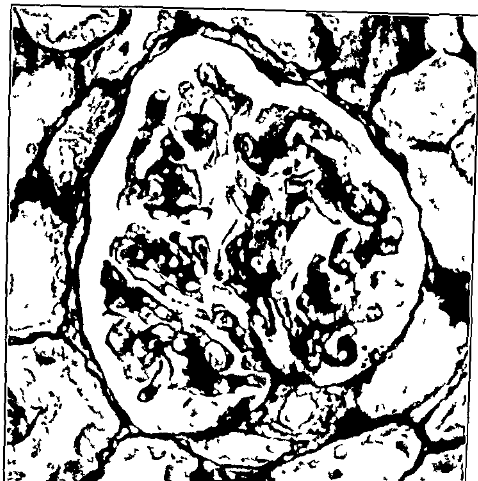


Figure 58

Glomerulus in Eclampsia

The loops of the capillaries are separate. The intercapillary spaces are reticulated and vacuolated. The tubular epithelium is uniform in height. There is dilation of the tubule lumens.



Figure 59

Glomerulus in Eclampsia

In addition to the discrete loops shown in the preceding two illustrations other features of eclampsia are seen in this illustration. The epithelial cells are present. The reticulation and vacuolation of the intercapillary space is shown. It will be better seen in the following two figures. There is no endothelial proliferation. (*McManus courtesy of Amer J Pathology*.)



Figure 60

Eclampsia—High Pou er of Glomerular Detail

The loops show a very fine vacuolation which is most marked between the loops but occasionall [illegible] haps a manife [illegible] nally empty [illegible] ath ognomonic of the condition It is suggested in the glomerulus wit [illegible] osin or an aniline blue stain It can only be made out definitely in my experience with the PAS method (*McManus courtesy of Amer Jour Pathology*)



F g re 61

Glomerular Detail Eclan psia

Th s h gh po e ph om crograph shows the re culat on and acuolat n of the intercap llary
space Th s o be compared the norm al appearance of the same area n figu e

Chapter 8

ACUTE PYELONEPHRITIS THE TOXIC NEPHROSES ACUTE TERMINATION OF CHRONIC RENAL FAILURE

ACUTE PYELONEPHRITIS

THE importance of acute pyelonephritis lies in the recurrent and permanent damage which results rather than the occasional fatality of the acute episode It was known for many years that acute inflammations of the kidney occurred However it was thought that no parencyhmal damage was done (the term pyelitis was more used than pyelonephritis) The tendency to chronicity went unrecognized The origin of chronic renal disease in pyelonephritis was first emphasized by Longcope[67] The cases collected by Weiss and Parker formed a convincing series in which chronic renal failure could be traced back to acute pyelonephritis[11]

The extremes of life and pregnancy appear to furnish most of the cases of acute pyelonephritis In infancy and childhood pyelitis has been recognized to be common as a variety of febrile illness frequently obscure and not recognized without urine examination In old age the prostatic difficulties of the male make the condition more common than it is in the female Old pelvic inflammation with scarring or postoperative pelvic adhesions after hysterectomy account for a share of the cases in the elderly female In other instances in both sexes no obvious mechanical obstruction to the flow of urine can be seen

The route of infection in many instances appears to be the ascent of an inflammation and infection from the lower urinary tract The factor of urinary stasis seems important in the obstructive cases mentioned and in those occurring during the pregnancy when the ureters are dilated A feature furthering the idea of obstruction is seen in the coincidence of acute pyelonephritis and hydronephrosis Renal ureteral and bladder calculi are commonly associated with acute pyelonephritis and may have a causative relationship

In other cases the pyelonephritis may be seen without any lower renal tract infection In these cases it is supposed that the organisms have been introduced into the kidneys by the blood stream or by lymphatic connections The lymphatic connections of the right kidney to the cecum and ascending colon are said to be well developed There is some suggestion that the ascent of an infection from the bladder to the kidney may be by way of the peri ureteral lymphatics[13]

The organisms cultured most frequently from the urine in acute pyelonephritis are members of the Coli Aerogenes group Streptococci of the fecalis type and the white staphylococci appear in other cases It has been emphasized that there must be a communication between the interstitial

inflammation and the renal passages before the organism can be cultured from the urine. Many cultures may then be necessary before the organism is grown from the urine despite the diffuse infection of the kidneys. This feature of the necessity for repeated cultures may be more important in the chronic renal infections than in the acute.

The disease may affect one or both kidneys. When both kidneys are involved, the degree of infection may differ in the two kidneys. When the kidney is misplaced at the pelvic brim or lower than normal, there is a marked tendency for the abnormally situated kidney to be the site of a pyelonephritis; the other one may be spared the infection.

The clinical features are chiefly those of an infection anywhere. Fever, leucocytosis and pallor are similar. It has been suggested that the leucocytosis may be high for the clinical condition of the patient. Dysuria is not constant. A bacteremia may occur during the course of the pyelonephritis. The organism may suggest the urinary tract infection if it is cultured from the blood. There is a striking tendency for anemia considering the briefness of the clinical course.[10]

In a large proportion of the patients with this disease there is pain in the loins. Sometimes tenderness may be elicited only after deep palpation or punching. The most consistent finding is pyuria with clumps of pus cells being almost diagnostic. Even in the fatal cases there is not consistently an azotemia. The blood pressure is not elevated as a rule. Death in these cases of acute pyelonephritis is seldom renal in origin. The development of an overwhelming infection with septicemia and metastatic abscesses in the various organs ushers in the end in some cases.

The gross appearances will vary with the degree of involvement. Most commonly there are fine linear yellow streaks running from the pelvis through the cortex and medulla. Small abscesses may be formed in the cortex. There is frequently an obvious infection of the pelvis. This may dominate the gross appearance. One can understand easily the older idea that the disease was restricted to the pelvis. It cannot be overemphasized that every pyelitis is in fact a pyelonephritis.

Microscopically there is an acute interstitial inflammation in the kidney. Destruction of tissue is obvious where the inflammation is most marked, but less striking is the alteration of renal structure where the infection is spreading and dissecting apart the nephrons. In the cortex the inflammation surrounds glomeruli to produce a peri glomerulitis.[11] This resembles in location the early infiltration of leukemia or a rare carcinoma in the kidney and suggests involvement of a lymphatic space. The spread of the inflammation to the glomerulus and its adhesion with subsequent fibrosis can be seen in any case of some duration (cf. p. 124).

Finally, it might be worth while to point out that acute pyelonephritis is extremely frequent, perhaps the next frequent infection to the upper respiratory tract group.[12] Pyelitis, that is pyelonephritis, is seen in 1 to 2 per cent of all pregnancies. A follow up of 30 cases ten to eighteen years

after bilateral acute colon bacillus pyelonephritis showed 2 with hyper tension and 7 with clinical evidence of urinary signs of renal impairment [18]

TOXIC NEPHROSES INCLUDING SULFONAMIDE

Various heavy metals as mercury and fat solvents such as ethylene glycol damage the kidney severely The tubules show the greatest change (Fig 62) As a rule the proximal tubules are chiefly involved but some poisons used in experimental studies of the kidney *e g* uranium can injure the distal convolutions It is probable that the involvement of the lipid containing mitochondria by all these poisons is the basis for the necrosis and retrograde changes seen microscopically Oliguria and anuria are the *rule It has been suggested that complete re absorption of the glomerular* filtrate is responsible for this [9] There is likely the additional feature of *reduced renal blood flow*

Some sulfonamides are acetylated on excretion and may precipitate out as crystals if the volume of urine is not at least 2500 cc daily Their pre cipitation in the collecting tubules may cause an obstruction There is an element of cellular damage to the tubules in fatal cases The microscopic picture shows many of the features of the crush kidney There is fre quently hypotension at some stage in the clinical course Hemoglobinuria when present completes the resemblance The clinical course is sufficiently like the crush syndrome for Lucke to term the condition Lower Nephron Nephrosis *For reasons described on page 94 this appears to* be an oversimplification

Rarely the allergic manifestations of sensitivity to sulfonamide in the skin or elsewhere are complicated by an acute renal failure The picture microscopically is quite distinctive It is worthy of mention because acute glomerulonephritis and periarteritis nodosa are said to be allergic manifestations and this type of sulfonamide injury is quite unlike either

The kidneys are swollen and congested weighing up to 300 grams each Microscopically the glomeruli and blood vessels appear normal There are areas of fatty change in the tubular epithelium and fat in some of the swollen tubular basement membranes A striking interstitial inflammation *with lymphocytes plasma cells* and eosinophiles is present in all sections of both kidneys (Fig 63) There are no eroded casts to account for this

ACUTE TERMINATION OF CHRONIC RENAL DISEASE

Diseases such as pyelonephritis and glomerulonephritis which have an acute origin and frequently a chronic course *may have the longer course* terminated by a recrudescence of the acute phase Somewhat more com mon is the appearance of the features of the crush *syndrome or post* hypotensive uremia in the later stages of chronic renal failure The basis for this combination of events is worth consideration

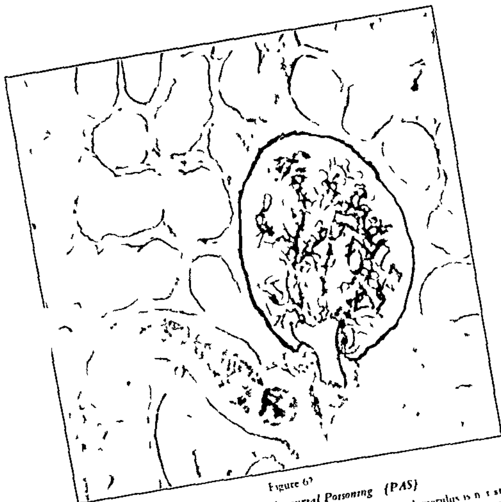


Figure 67

Toxic Nephrosis. Mercurial Poisoning (PAS)

This is from a case dying ten days after ingesting mercury The glomerulus is not striking abnormal The calibre of the loops may be reduced The principal lesion is seen in the tubules Several contain granular debris There is a deeply coloured cast in one All the tubules are dilated with flattened epithelium The tubules are separated slightly from one another perhaps by interstitial edema

This section is typical of the toxic nephroses The damage seems restricted to the tubular epithelium in the case of mercury to the proximal convolutions

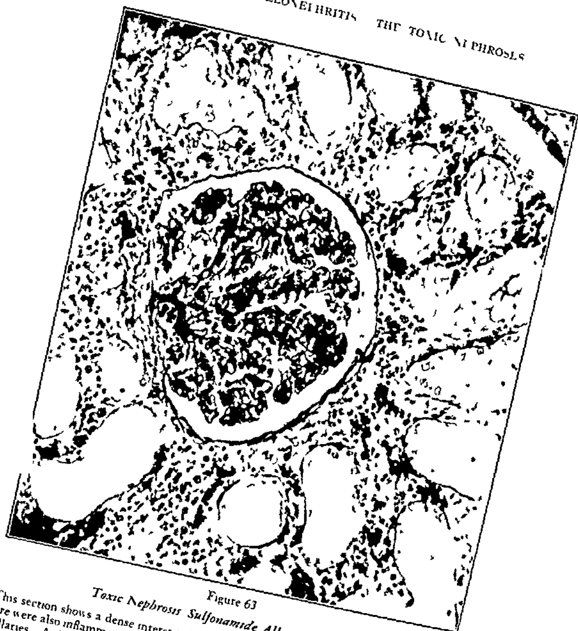


Figure 63

Toxic Nephrosis Sulfonamide Allergic Reaction

This section shows a dense interstitial inflammation in a case of sulfonamide intoxication There were also inflammatory cells interstitially in the heart and vascular necroses in cerebral capillaries A skin eruption with blood eosinophilia corroborated the allergic features present in the history

This section has been stained with the PAS method after hematoxylin and eosin The red blood cells show up darkly in the photomicrograph This feature is responsible for prominence of the capillaries in the glomerulus and in the interstitial tissue The epithelium of the tubules is flattened The tubular lumens are dilated

The usual sulfonamide kidney injury results from precipitation of crystals as a result of reduced urine volume



Figure 64

Venous Thrombus. Lipoid Nephrosis

The thrombus in the vein is conspicuous. The glomerulus has a reticulated intercapillary space. The atrophied tubules in the center upper part of the picture are a sign of long standing disease. There is increased interstitial tissue with cellular infiltration.



Figure 65

Venous Thrombus: Malignant Hypertension

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It is apparent from a study of various types of acute and chronic renal disease that the tubulo venous thrombi and interstitial casts of the crush syndrome can be seen in many kidneys (Figs 19 45 48 64 65) Similarly the dilated tubules with flattened epithelium and the dilated capsular space with granular contents has been recognized since the description of Volhard who called this the picture of uremia [30] Zondek has emphasized the crush like termination of some chronic renal diseases unfortunately without histologic description The sudden deterioration of the clinical condition is said to be striking terminating fatally with oliguria and anuria within a week The precipitating factor is not always obvious In one personal case of interval glomerulonephritis with cardiac hypertrophy there was a fatal termination following sulfonamide medication for an acute upper respiratory infection The features of the crush lesion were present in addition to those of the older disease

The particular tendency of the damaged kidney to suffer added injury may be explainable upon a structural basis A degree of vascular sclerosis could magnify the effect of periods of renal ischemia during shock The complete explanation of this feature of increased susceptibility should be of clinical and pathologic value

Chapter 9

CHRONIC RENAL FAILURE
THE PROBLEM OF THE SHRUNKEN KIDNEY

CHRONIC RENAL FAILURE

THE signs and symptoms of chronic renal failure may result from any long standing kidney damage—the rare case of chronic glomerulonephritis the usual chronic pyelonephritis, polycystic kidneys with extensive involvement of the parenchyma and the small proportion of arteriolar nephrosclerosis in which renal failure develops All show the same clinical features There is a general similarity of signs and symptoms which represent inadequacy of kidney function rather than indicating to any presently recognizable degree the type of original injury

It is suggested that two thirds of the functioning ability of the kidneys must be lost before signs of renal insufficiency become apparent [2] There may be a loss of the portion of the total number of nephrons or the functioning ability of the nephrons must be reduced to that degree In some cases of chronic pyelonephritis it seems that more than two thirds of kidney substance has been lost The kidneys are represented by nubbins of tissue weighing perhaps 90 or 100 grams together with some of that being fibrous tissue Perhaps the speed at which the loss occurs is important, rate being important in so many pathologic developments

Anemia is the most constant clinical feature of the renal invalid In any center in which the treatment of anemia is prosecuted vigorously it is a common experience to find a proportion of hematology clinic visitors terminating in uremia The mechanism for the production of the anemia is unknown It has been suggested that the anemia is the result of the accumulation of phenols and a toxic action on the bone marrow [41] Microcytic hypochromic anemia is the rule and the red blood cell count reflects in reverse degree the accumulation of nitrogenous wastes

The non protein nitrogen remains within normal limits until the degree of loss of function and functioning tissue is considerable This retention of urea and similar materials is responsible for the term ' uremia ' by which the condition is known In usage uremia may appear to be restricted to the end stage with the striking coma convulsions vomiting and disturbances of respiration which usher in the final stages and herald its termination Actually the term describes the whole depressing sequence commencing at the point at which the accumulation of non protein nitrogen begins When the NPN passes 100 mgm per cent death may be near [8] Uremia can and does appear rarely without a major elevation in the NPN but this is so uncommon as to deserve no more than mention

Accompanying the accumulation of the products of protein metabolism

and sometimes preceding it there is a loss of concentrating ability by the kidneys A urine specific gravity above 1 010 is seldom reached There may be a reduction in the total volume of urine produced Nocturia reveals the continual activity of the kidney With the retention of urea this failure of concentrating ability is the basis for one of the most popular tests of renal function Diodrast and Inulin clearances are reduced before the loss of concentrating ability furnishing a method more useful in following cases of renal disease than in making the initial diagnosis The first untoward sign noticed by the patient usually is nocturia The loss of concentrating ability during the progress of renal failure marks another milestone in the development of the disease The excretion of such materials as phenol sulphonepthalein (PSP) is reduced

Associated with anemia the accumulation of waste products and the loss of concentrating ability there is frequently the important feature of arterial hypertension In some cases the hypertension dominates the picture and the patient presents himself to the physician because of heart heart failure or a cerebral accident or encephalopathy The antecedent kidney disease is revealed only upon questioning and examination The mechanism of this type of hypertension is unknown as are the rest of the cases of hypertension It is accompanied consistently by arteriolar sclerosis in the kidney The degree of vascular disease noted upon careful study may be correlated with the height of the blood pressure Renal ischemia is the obvious result of the arterial and arteriolar disease The fashion in which this causes hypertension if it does cause it is not known

The termination of uremia of long standing is marked by coma increased neuromuscular irritability as manifested by convulsions slow deep breathing or stertorous and periodic breathing pericarditis and vomiting[43] The degree of these features varies from case to case and some of them may be missing Skin changes may be striking and the uremic frost—precipitation of urea on the skin as it is excreted by the glands of the skin—is common A yellow color in the exposed parts of the skin may be due to an oxidization of the retained urinary chromogens Uremic colitis with ulceration produces a terminal diarrhea sometimes bloody ushering in the end The final cardiac arrhythmias reproduce in many respects the changes following experimental potassium poisoning[4,42]

It can be seen from the preceding discussion that the sequence of chronic renal failure presents a complex picture It may be an over simplification to compare death in uremia to the death of the aging bacterial culture as Harrison and Mason have done There is this truth in the analogy that both organisms appear to die in an environment poisoned by the products of their own metabolism

THE PROBLEM OF THE SHRUNKEN KIDNEY

The kidney that has been injured to a considerable degree over a long period of time tends to lose the distinguishing features of specific disease

which are so prominent in the earlier acute phases There is a general similarity of appearance whether the original disease was glomerular tubular interstitial or vascular Eventually all the component structures vessels nephrons and interstitial tissues—become distorted in a complicated appearance The distinction between these different patterns of disappearance is the problem which confronts the pathologist in the shrunken kidney

It is strikingly like the situation in the body as a whole in nutritional cachexia The condition may result from a variety of absorptive errors—anorexia nervosa pituitary insufficency inanition difficulty in absorbing food and so on Whatever the original cause the end result is about the same While the original injury or error may involve one body system at beginning of the process with the advancement of the cachexia the primary process may be difficult to identify A small lesion may be identified as the basic one but like beauty this proves often to be in the eye of the beholder

We have already spoken of the three main types of renal disease nephron involvement vascular involvement and interstitial tissue involvement Nephron changes may result from vascular disease as was described under arteriosclerosis (p 60) The main process of nephron loss follows the pattern of glomerular wrinkling and obsolescence In turn it is generally recognized that vascular disease follows nephron and interstitial tissue disease (p 56) Less well recognized is the fashion in which interstitial tissue changes constantly and inevitably follow and accompany vascular and nephron disease

With either primary vascular or nephron disease there are scars in the renal tissue and changes in the urine such as albuminuria which make the urine a suitable media for bacterial growth At the same time the renal scars distort the intra renal lymphatics and interfere with adequate nutrition of the renal tissue Histologically the presence of the lymphocytes in sections from nearly every variety of chronic renal disease could result from the interstitial tissue disease The original disease in the earlier cases of chronic glomerulonephritis can be recognized by the characteristic glomerular lesions but in most cases the vascular and interstitial processes supervene and dominate the picture

The whole picture corresponds to a vicious cycle Vascular disease affects the nephrons and interstitial tissue These alterations produce further changes in turn Eventually the accumulation of insults seriously distorts the kidney The remaining nephrons are unable to carry the load and renal failure results Signs of renal failure—hypertension and anemia—result from and may themselves alter the scarred and shrunken kidney

One clear cut case in which distinctive clinical features made this reconstruction possible has lately come to autopsy at the Medical College of Alabama The patient was forty years of age and had a history of an acute

episode of typical glomerulonephritis some six years previously This was followed two years later by a nephrotic episode characterized by anasarca reversal of the A G ratio in the blood anemia and a slight hypertension The edema improved but persisted for the remainder of the patient s life This was marked also by signs of renal failure and complicated by increasing evidence of urinary tract infection

At autopsy there was chronic cystitis ureteritis cystica chronic pyelonephritis cardiac hypertrophy and terminal lobular pneumonia Microscopically in the kidneys the picture was mainly that of a chronic pyelonephritis with marked interstitial inflammation vascular sclerosis and areas of atrophy and hypertrophy A few of the more normal glomeruli presented the fixed medium patency of the glomerular loops (Fig 74) described in nephrosis by Shaw Dunn [2]

Unless the original episodes were a pyelonephritis of hitherto undescribed variety it seems that the sequence of events was pyelonephritis supervening upon glomerulonephritis It is likely that the frequency of autopsy diagnosis of pyelonephritis may depend upon the same sequence since many of the histories suggest glomerulonephritis Ehrstrom believed that mixed forms of pyelonephritis and glomerulonephritis occur in both acute and chronic forms [3] Bell described a case of pyelonephritis supervening upon glomerulonephritis [9]

Chapter 10

CHRONIC PYELONEPHRITIS

THIS is the most prevalent of all renal diseases by autopsy All or nearly all adults at autopsy will show a microscopic focus of chronic pyelonephritis and in many the degree of the disease is marked Renal failure as a result of pyelonephritis is not uncommon and hypertension associated with chronic pyelonephritis is frequent In many cases of chronic glomerulonephritis the survival of the patient is long enough to allow the development of pyelonephritis of such a degree as to overshadow the original disease

The association of chronic pyelonephritis with hypertension has been shown clinically[60] and at autopsy [1*] Many cases of essential hypertension are found to have abnormalities of the urinary tract [94] In most of these a chronic pyelonephritis is recognizable clinically in others the presence of the disease is inferred from the urinary tract abnormality and proven at autopsy Retrograde pyelography must be used for the demonstration of the course and caliber of the ureters and in the search for the finger like projections into the renal parenchyma which the pelvis and calcyces may show In others the distortion of the pelvis is obvious even with intravenous urography

The experimental production of hypertension upon the basis of urinary obstruction and infection has not been uniformly successful [66] Part of the difficulty in this may be the upright position of the human and the lack of a suitable experiment animal Some 80 cases of unilateral pyelonephritis with hypertension relieved by removal of the diseased kidney can be found in the literature Unfortunately many of these cases have been reported before the necessary two years have elapsed following operation This is the critical time of observation required before permanent improvement can be claimed [96] Those cases in which the other kidney is not diseased and in whom some significant hypotensive effect is produced by thiocyanates and similar drugs may be improved or even cured by the removal of a pyelonephritic kidney

There is no doubt that many cases of human hypertension have chronic pyelonephritis and that many cases of chronic pyelonephritis have hypertension If the clinical notes in the cases of Bell are adequate and do not represent agonal values of blood pressure it seems clear that some cases of pyelonephritis do not have hypertension The peculiarity present in the cases of pyelonephritis associated with hypertension has been studied by several groups of workers

Weiss and Parker felt that the hyperplastic arteriosclerosis was the determining factor in the elevation of the blood pressure [111] This takes the form of the duplication of the cells of the arterioles presumably smooth

muscle cells Bell points out that this arteriolar change may be the result rather than the cause of hypertension * Diffuse arterial disease according to Bell is a more frequent concommittant The diversity of views indicates that much remains to be done on the problem In passing it may be said that the granular cells of the renal arteriole are not numerous in many cases of chronic pyelonephritis with hypertension

The protean antecedents of many cases of chronic pyelonephritis have been mentioned previously (p 111) There does not appear to be any single feature in the history which would make one think of chronic pyelonephritis unless it is a pelvic operation or infection a clear cut history of previous urinary tract infection or pyelitis during pregnancy or in childhood The individual usually shows hypertension Even today with the emphasis on pyelonephritis only the enthusiast would treat every case of hypertension as a chronic pyelonephritis It is wise to consider pyelonephritis a possibility until ruled out

It has been pointed out by Weiss and Parker that the patient with hypertension and chronic pyelonephritis who presents him or herself to the clinician has frequently been seen by other specialists There may be history of sub normal health or even of chronic invalidism The pallor of these patients is striking in many cases indicating the anemia of chronic infection and azotemia

It is not always possible to separate clinically acute subacute chronic and chronic healed pyelonephritis Most of the cases of hypertension are actually in the healed chronic stage The original infection has subsided the earlier pyuria is passed and the sequelae chronic invalidism and hypertension—take the prominent clinical rôle With the hypertension there are cases with cardiac failure Despite the clinical difficulty of separation into stages the pathologist in most instances is able to identify the progress of the disease This appears to be another example of the pathologist taking over the clinical diagnosis and progress of the disease much as intercapillary glomerulosclerosis (*cf* p 146)

It is the opinion of some that the sub acute stage represents a chronic active condition The acute infection is present at the time that the scarring resulting from the older infection is marked Clumps of pus in the urine low grade temperature and leucocytosis represent the acute process Anemia elevated NPN and hypertension mark the chronic renal injury

The clinical diagnosis of chronic pyelonephritis may be difficult or easy Hypertension even in childhood should make one consider the possibility of pyelonephritis [81] The patients may appear in excellent health even though hypertension and chronic pyelonephritis are present [19] Abnormalities in the urine aid in the diagnosis but it may be extraordinarily difficult to demonstrate pus cells and especially bacteria Many examinations of the urine may be required for positive culture

In chronic healed pyelonephritis the urologist and the radiologist combine to establish the diagnosis The internist may see hypertension or

chronic renal failure but for *determining the etiology* other specialists are necessary

All cases of hypertension do not show radiologic evidence of urinary tract abnormality *Of those who do not* many have urinary evidence of pyelo nephritis Radiologic evidence of urologic disease was pointed out to be no more frequent than arthritis duodenal ulcer or gall bladder disease in a series of hypertensive patients These data were taken to mean that urinary tract abnormality was insignificant in hypertension an obvious non sequitur [86]

The kidney severely involved by pyelonephritis over a period of years will as a rule be small and scarred The capsule strips with difficulty Frequently the surface shows depressed firm areas alternating with thy roid like nodules of brown color It is rare to have intervening tissue of normal appearance The cut surface retracts The cortex is thin or ab sent When any cortex remains fine scars traverse cortex and medulla In many cases the pelvis is dilated with a chronic pyelitis perhaps of the cystica variety Calculi may be present Thyroid like areas may be seen in the cortex Abscesses of small size represent activity of the infection

The gradual progression of fibrosis into the tuft of the glomerulus during the acute phase of pyelonephritis has been mentioned (p 111) This is *illustrated in figures 66 to 69 The end result is a fibrous knot which re* mains in an open capsular space Very frequently the glomerulus is de stroyed and not a trace of it is left The hyaline knot form is a character *istic and pathognomonic appearance Dawson and Langley recognized the* importance of partial fibrosis of the tuft as an indication of pyelonephritis and pointed out that the lesion was described quite clearly by Fahr and Schoen [2]

The thyroid appearance of portions of the surviving cortex in the gross is represented by groups of colloid casts in the sections (Fig 70) The ap pearance microscopically is much like thyroid tissue groups of dilated or atrophied tubules being full of a hyaline material In the rest of the kidney tissue areas of scarring and atrophy alternate with sets of oversized and *dilated tubule units (Fig 71) In the chronic stage* there is progressive disappearance of glomeruli by fibrosis of the special sort with foci of chronic inflammation In the healed chronic variety the lymphocytes are few or absent and the progressive glomerular disappearance is not seen

In both the chronic and the healed chronic stages or types of pyeloneph ritis the vascular lesions particularly the arterial ones are striking (Fig 72) Most of these have already been mentioned—endarteritis obliterans and hyperplastic or disuse alteration of the arterioles In some cases the arterial lesions predominate and it is difficult to recognize the basic disease pyelonephritis or arteriolar nephrosclerosis

Severe pyelonephritis can occur in chronic form without hypertension Even the arterial and arteriolar alterations may be indistinguishable from those cases in which hypertension is marked It is not usual however to



Figure 66

Glomerular Obsolescence in Pyelonephritis. Beginning

This illustration is intended to show an early stage of glomerular obsolescence. There is an adhesion of the glomerulus to the capsule at the top. Many atrophied tubules are seen. There is an increase in the interstitial tissue with many inflammatory cells. The macular segment of the distal tubule is still attached to the glomerular root. Tubular atrophy is not yet marked.

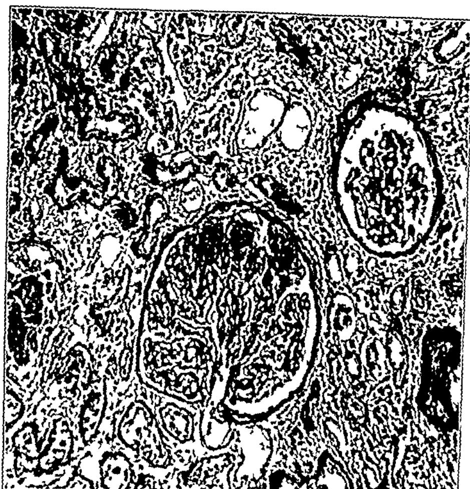


Figure 67

Later Stage of Glomerular Obsolescence

The fibrous tissue is seen extending into the glomerulus from above The other features of interstitial inflammation and atrophied tubules can be seen also This sort of lesion in pyelonephritis was recognized by Fahr by Schoen and by Davson and Langley [21] *Beginning atrophy of the tubule of the nephron is seen in the tubule at the left above the glomerulus* The macular segment of the distal tubule is separated from the arteriole There is a cast in the tubule at the left



Figure 68

Late Stage of Glomerular Obsolescence Pyelonephritis.

The glomerulus is nearly completely fibrosed. The capsular space is empty. There is atrophy of some of the tubules and hypertrophy of others. The interstitial tissue is increased about the atrophied tubules. The alternation of hypertrophy and atrophy of tubular segments is seen frequently in chronic renal diseases as Oliver and Lund describe.[41]

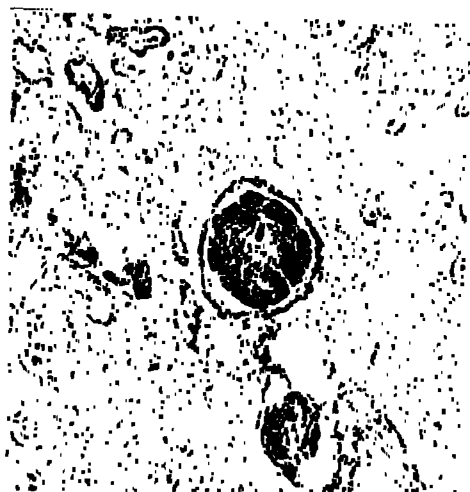


Figure 69

Late Stage of Glomerular Obsolescence. Pyelonephritis

The glomerulus in the center of the field is completely fibrosed There is a residual space around the fibrous glomerulus The marked atrophy of the tubules can be made out There is an increase in interstitial tissue The margins of two thick-walled blood vessels can be made out above and below

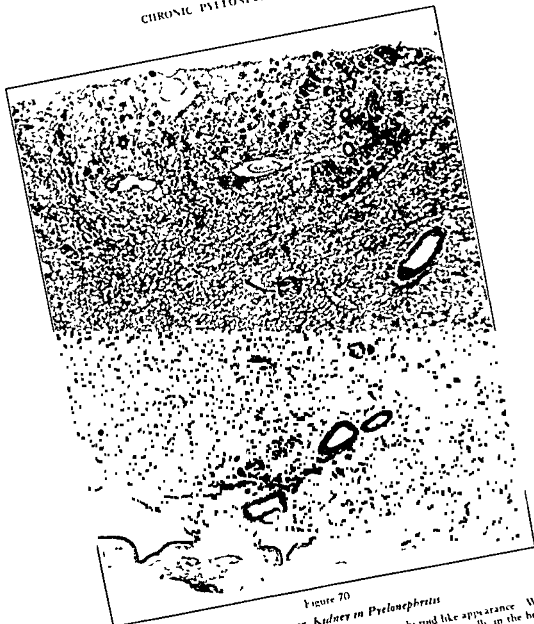


Figure 70

Very Low Power, Kidney in Pyelonephritis

The aggregated tubules containing colloid casts produce a thyroid like appearance. Weiss and Parker indicated the frequency of this lesion in pyelonephritis especially in the healed chronic stage. Areas of fibrosis and tubular collapse can be seen. The vessels are prominent appearing as circular and oval structures. In the cortex they are seen best near the thyroid like areas and in them

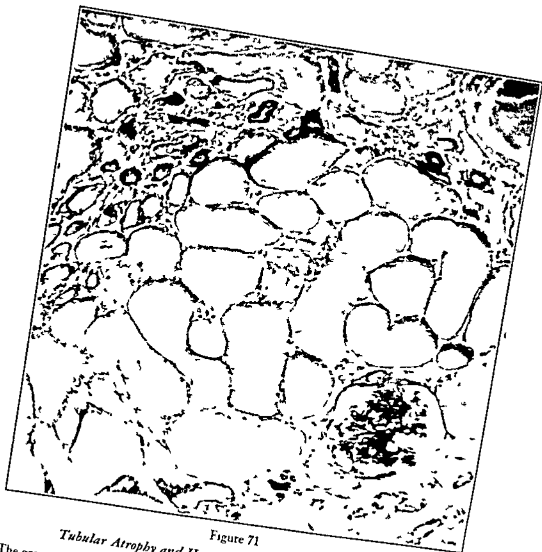


Figure 71

Tubular Atrophy and Hypertrophy in Chronic Pyelonephritis

The group of tubules about the glomerulus in the lower right are probably part of the one nephron The glomerulus is adherent to the capsule in several places and partially fibrosed The tubules are hypertrophied in part and nearly obsolete in other areas



Figure 72

Kidney in Pyelonephritis. Low Power of Cortex

This area shows a number of glomeruli and vessels. The glomeruli show varying degrees of fibrosis but there is some increase in connective tissue in all the glomeruli. Two obsolete glomeruli are seen and a portion of one other. The vessels show sclerosis. There is tubular atrophy and increase of interstitial tissue.

This sort of section is important from several viewpoints. In the first instance, it shows that there is involvement of the glomerulus in pyelonephritis. Secondly, the association with vascular disease is quite constant if not invariable.

find this disease in severe degree in both kidneys without hypertension. A certain number of cases of unilateral pyelonephritis have had nephrectomies without relief of hypertension even when the other kidney was normal by all clinical tests.[96] This resembles the persistence of hypertension in some experimental Goldblatt animals. Hypertension of long duration is not relieved by removal of the clamp or of the clamped kidney.[33] The importance of an additional factor in the development of hypertension in pyelonephritis of chronic sort, whether the factor is vascular or humoral, seems obvious. Pyelonephritis is twice as frequent as normal in Negro women dying with hypertensive heart disease. This must have some significance.[29]

Benign interstitial nephritis is seen in acute febrile diseases such as scarlatina, diphtheria and rheumatic fever. The interstitial connective tissue is infiltrated with lymphocytes, plasma cells and monocytes. The term "benign" suggests that the process leaves no residue. This is largely supposition and some cases of benign interstitial nephritis may precede chronic pyelonephritis. I have one such case in my collection. Rheumatic fever terminating as clinical "malignant" hypertension showed the lesions of chronic pyelonephritis. These have been described by Craciun for chronic rheumatic glomerulonephritis.[20] The possibility has been mentioned by others.[7]

Chapter 11

CHRONIC GLOMERULONEPHRITIS

About 4 per cent of the cases of acute glomerulonephritis continue without any obvious remission terminating fatally in from five weeks to two years. These "subacute" cases are marked by massive and persistent edema, continued albuminuria and final hypertension. Purulent pneumococcal infections of the serous cavities may be present, causing death in some cases. Hypertension need not supervene in those cases in which the infection of pleural cavity or peritoneum is rapidly fatal.

Some cases of this type of glomerulonephritis have a relatively inconspicuous or brief acute episode which is overlooked. The appearance of these cases as chronic renal disease without hematuria, with massive edema and albuminuria and with reversal of the albumin globulin ratio in the blood, is responsible for the clinical term "nephrosis." At autopsy most of these cases are chronic glomerulonephritis with crescent formation predominating. All of the cases which are not of this frank type do show some glomerular alteration, adhesions or localized basement membrane change. Large proximal convoluted tubule cells loaded with lipoid in which cholesterol can be demonstrated are seen also (Figs. 73 and 74). During life the urine shows much of this cholesterol, the adjective "lipoid" being used to designate the disease.

Ellis and Wilson point out that about 10 per cent of the cases of acute glomerulonephritis have a persistent albuminuria after apparent recovery from the acute attack.[33] Recurrent attacks with the clinical features of the original episode are common in some of these. Survival in these cases is usually limited to six to eight years. The large majority of these cases of persistent albuminuria after an acute attack do well for ten, fifteen, or twenty years. Seventy per cent of these cases survive the acute attack for more than ten years, 30 per cent for more than twenty years.

The clinical picture at the terminal episode is, as the British workers have pointed out, coincident with the development of a persistent and progressive hypertension.[23] Without the history of the acute attack the terminal picture suggests "malignant" hypertension. The picture of renal failure, edema, nocturia, polydipsia, headache and nausea, is quickly replaced by the results of the hypertension, cardiac failure and retinal hemorrhages. Survival is not extended past two years from the recrudescence of the old disease. It has been my impression that the features of acute hypertension are so successfully mimicked pathologically that "malignant" hypertension has been the anatomic diagnosis (Figs. 75 and 76).

A special variety of glomerulonephritis with no history of preceding infection has been described by Ellis and Wilson.[31] It is marked from the

onset by edema and lasts for two to ten years with a 95 per cent mortality This is called type II glomerulonephritis by these workers The more usual variety forming the basis for this description and that of the previous acute disease is called type I (Figs 77 to 81) The type II disease is characterized histologically by thickening of the basement membrane and intercapillary hyaline deposit resembling the lesion of Kimmelstiel and Wilson in diabetics (*cf* p 146) Crescents are absent the disease affects the glomeruli in a remarkably uniform fashion and tubular hypertrophy is not marked

Two main impressions are given by this type II glomerulonephritis I believe it can be recognized as an entity of infrequent occurrence Secondly the similarity in histologic appearances to the diabetic intercapillary glomerulosclerosis strongly suggests that some common etiologic factor will be found

It cannot be overemphasized that chronic glomerulonephritis is a diagnosis which the pathologist makes rarely these days The clinician uses the term constantly perhaps carelessly The kidney which has been severely damaged has a pathologic appearance which represents and reflects the original injury with the accumulated injuries of the other structures of the kidney consequent upon and associated with the progress of the disease (Figs 82 and 83) In making a specific diagnosis of chronic glomerulonephritis the clinician states the type of the original disease He postulates that sufficient indications are left in the kidneys for the pathologist to recognize it It should be recalled that in Case 23 of Bright s original report there were multiple calculi This suggests pyelonephritis



Figure 73

Glomerulus, Lipoid Nephrosis

This glomerulus is from a child with clinical lipoid nephrosis. The mesangium is reticulated. The loop at the extreme lower right has involvement of the capillary lumen. This was the extent of the glomerular lesions.

The tubules are generally flattened. That at the upper right shows granular cytoplasm. There is some thickening of the cells.



Figure 74

Glomerulus in Lipoid Nephrosis.

This glomerulus shows the small fixed patency of the glomerular capillaries This feature was described by Shaw Dunn The glomerulus is one from a case of "lipoid nephrosis" terminating in acute and chronic pyelonephritis

Actually, the entity of lipoid nephrosis may not occur Many of the cases which are [illegible]

reticulation of the mesangium is discussed in page 51



Figure 75

Hyaline Arterioles Chronic Glomerulonephritis

The upper two arterioles are contorted and hyalinized in part. The lower arteriole is thickened. A glomerulus is seen in part at the upper left; it is not abnormal. There is thickening of the tubule basement membrane. The interstitial connective tissue is cellular and increased



Figure 76

Hyaline Arterioles in Chronic Glomerulonephritis

Four altered arterioles are shown in the illustration Three are hyalinized the fourth is hypertrophied One normal arteriole is seen The increased interstitial connective tissue is surrounding altered tubules with thickened basement membranes

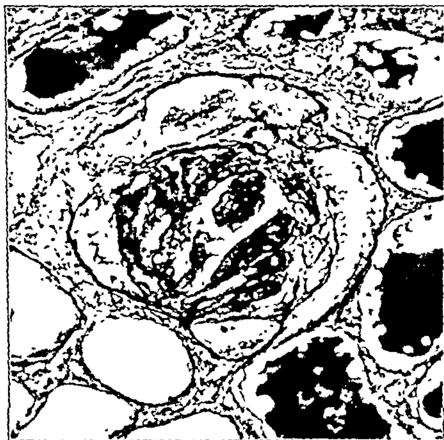


Figure 77

Chronic or Subacute Glomerulonephritis—Tubules in Crescent

This glomerulus is one from a case with a six months history. The capillaries of the glomerulus are occluded largely by fibrosis. The crescent in the capsular space is made up of ramifying tubules. The parietal basement membrane is lacking at the left. The tubules are dilated. Many contain colloid casts. There is increased interstitial tissue.

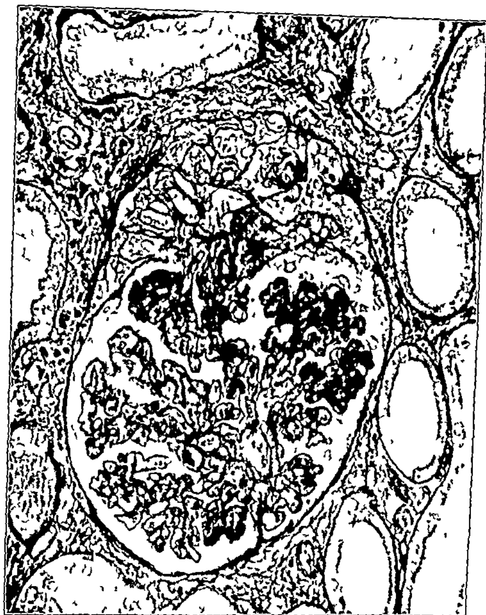


Figure 78

Crescent in Interval Glomerulonephritis

This glomerulus is from a case of interval glomerulonephritis All the glomeruli had some abnormality usually thickened basement membranes of the capillary loops Approximately 10 per cent of the glomeruli showed crescents There was a history of hypertension The heart was hypertrophied Death was due to a crush lesion complicating lobular pneumonia and lung abscess

The segment of capsular space occupied by the crescent shows ramifying tubules



Figure 73

Tubule Formation about Obsolete Glomerulus. Chronic Glomerulonephritis.

This obsolete glomerulus is surrounded by a halo of tubule-like structures. The remains of the parietal basement membrane can be seen in places. The tubules are remnants apparently of structures developing in the crescent. It is impossible to say whether they possess any functioning ability or not. Seriously distorted nephrons (some aglomerular) are seen in scarred kidneys. They may be related to new tubule formation.



Figure 80

Tubule Formation in Crescent Chronic Glomerulonephritis

This glomerulus is practically fibrosed The parietal basement membrane remains only in a small area at the upper left The capsular space is filled by fibrous tissue but in it a few tubule-like structures remain Even a fibrosed glomerulus such as this may be functioning to some degree but it seems unlikely The persistence of tubules in the crescent may be related to independant tubular activity of the type seen in the aglomerular nephron Oliver has found such aglomerular units in scarred kidneys



Figure 81

Fibrous and Cellular Crescent. Chronic Glomerulonephritis.

This is one type of glomerular obsolescence in glomerulonephritis. The space of Bowman's capsule has been filled in by cellular tissue. This has a fibrous and reticular framework. The parietal basement membrane is interrupted in many places. The glomerulus is fibrosed. No new tubules are left in this type of glomerular obsolescence. The proportion of this type of obsolescence to that shown in figures 77 to 80 might be important in residual functioning of the kidney.

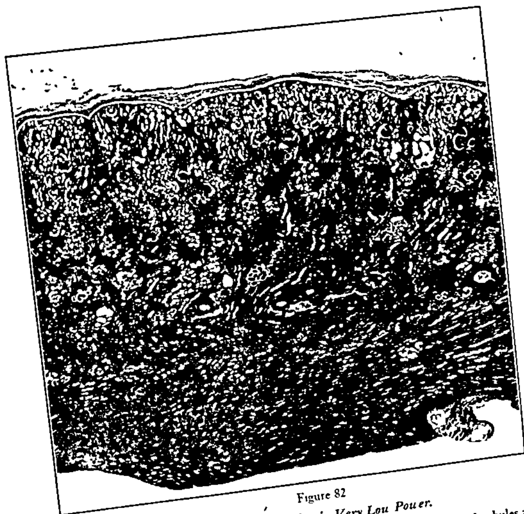


Figure 82

Chronic Glomerulonephritis, Very Low Power.

The capsule is thickened The cortical surface is nodular Groups of dilated tubules are seen In other areas tubular collapse can be seen Relatively few glomeruli are recognizable but crescents can be made out in these The vessels are prominent Groups of colloid casts are seen



Figure 83

Chronic Glomerulonephritis, Very Low Power

The cortex is not decreased in thickness The vessels are prominent Many colloid casts are recognizable Some groups of dilated tubules occur With close examination crescents can be seen in many glomeruli Other fibrotic scars appear

This is an earlier stage of glomerulonephritis than that of figure 82

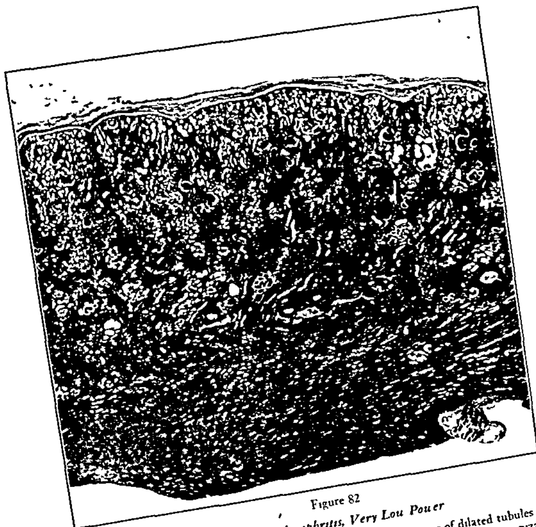


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Chapter 12

INTERCAPILLARY GLOMERULOSCLEROSIS POLYCYSTIC KIDNEYS

INTER-CAPILLARY GLOMERULOSCLEROSIS

(Kimmelstiel Wilson Disease)

The lesion of Kimmelstiel and Wilson *in the glomeruli of some diabetics* was probably intended originally as a pathologic description[95] Following the presentation of Kimmelstiel and Wilson it has been recognized that a number of diabetics of long standing, particularly mild ones will show inter capillary glomerulosclerosis associated with albuminuria retinitis edema hypertension and uremia The meaning of the term has gone from a pathologic description to a clinical syndrome A certain amount of argument is entailed in just this point[91]

Kimmelstiel and Wilson saw hyaline material which they interpreted as lying in the space between the capillaries of the glomeruli[54] With their methods—Mallory s aniline blue stain—they were not certain that normally there was an intercapillary space The position of the material suggested that it was actually inter capillary in situation Allen has reviewed a number of cases of intercapillary *glomerulosclerosis and believes* that the lesion is quite distinctive for diabetes[3] He states that the inter capillary glomerulosclerosis is seen more commonly in diabetes than any other lesion including those of the pancreas

The lesion is readily studied with the periodic acid Schiff s reagent (PAS) method (Figs 84 85 and 86) There is a difference of appearance of the glomeruli in diabetics in paraffin and frozen sections In the glomeruli of diabetics which do not show frank inter capillary glomerulosclerosis there is an *alteration of the inter capillary space with either method In frozen* sections the intercapillary space appears to be filled with a hyaline material which colors strongly with PAS The same intercapillary space in paraffin sections shows only a fine fibrillation All stages of transition between these appearances and the large nodules of hyaline distorting the glomeruli are seen in diabetics (Figs 87 to 90)

Grossly, there are no characteristic changes of intercapillary glomerulosclerosis, We have seen kidneys with the disease which have weighed 250 grams apiece and other cases with kidneys weighing 80 or 90 grams apiece I cannot be sure grossly that consistently there is any marked arteriosclerosis

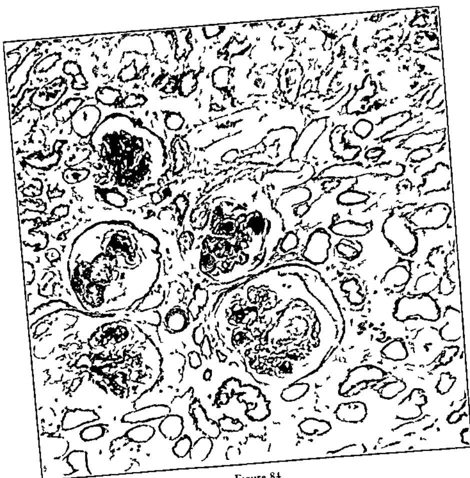


Figure 84

Intercapillary Glomerulosclerosis

This is a low power of the cortex in intercapillary glomerulosclerosis. Five glomeruli are [illegible] There is [illegible] seven year history of diabetes in this case of an aged female. [illegible]

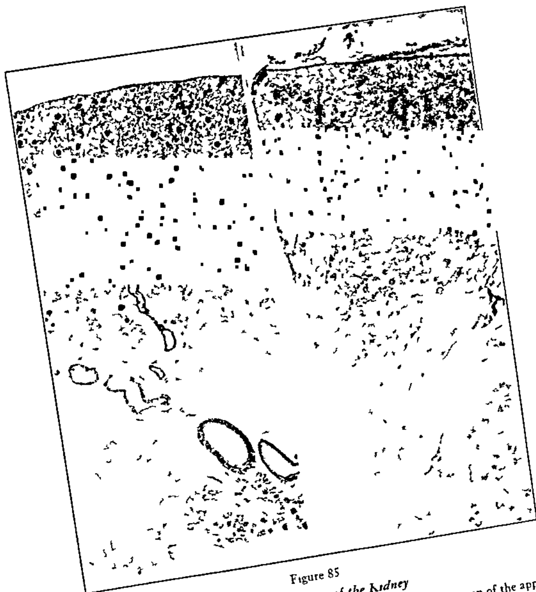


Figure 85

Low Power Views of the Kidney

The sections of the kidney shown above are intended to represent a portion of the appearance which one can make out with the lowest power of the microscope or with an inverted eyepiece. The kidney at the right is from a case dying in shock after severe wounding. The case at the left is a chronic glomerular disease associated with diabetes mellitus. The branching of the vessels can be seen in both instances, best at the left. The glomeruli at the left are thrown into prominence because of the deposit of a hyaline material in them.



Figure 86

Intercapillary Glomerulosclerosis High Power of Capillary Loop

The center of the loop is filled by a laminated hyaline material The lumen of the capillary is external to the hyaline material The capillary has an external but no internal basement membrane This appearance is the late result of the deposit of hyaline material in the intercapillary space (*cf* Fig 5) Nuclei can be seen in clefts between the laminæ Reticulin is said to be demonstrable in these clefts The material infiltrating the glomeruli in intercapillary glomerulosclerosis is not derived from an internal basement membrane Unlike the glomerular basement membrane it is removed by pectinase digestion



Figure 89

Intercapillary Glomerulosclerosis Low Power of Cortex (P 15)

This area shows several glomeruli in various late stages of obsolescence associated with the deposit of hyaline material of the glomeruli Secondary changes in the tubules have resulted in thickened basement membrane around many tubules

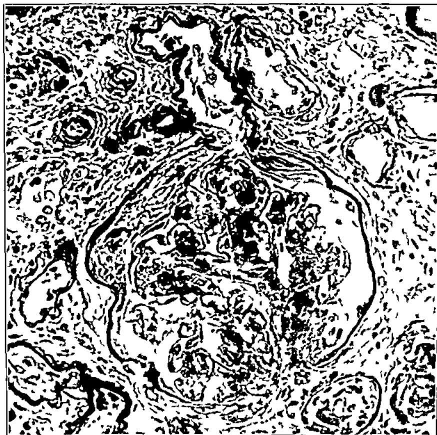


Figure 90

Glomerulus in Intercapillary Glomerulosclerosis

This glomerulus shows the hyaline intercapillary material forcing the capillaries peripherally. As usual a peripheral basement membrane can be seen in the capillaries. The central limitation of the masses is shown in figure 86.

The effects of the glomerular injury are seen in the thickened basement membrane of the tubules and the increased interstitial tissue. Casts are seen in the tubules. A thickened arteriole is seen in the left upper quadrant. An anomalous finding is the fibrous material in a portion of the capsular space.

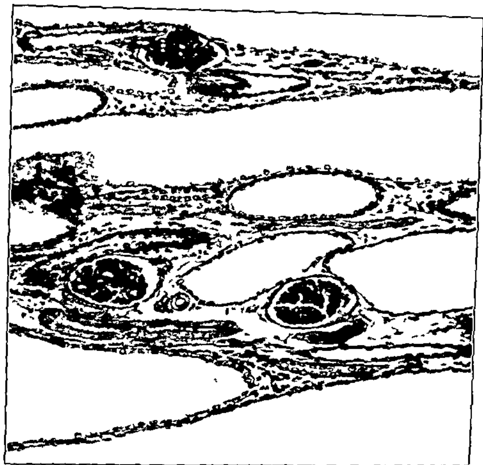


Figure 92

Polycystic Kidney Infant

A segment of kidney tissue is shown Three glomeruli are recognizable The rest of the tissue has been replaced by dilated cystic tubules This condition is not compatible with post uterine life if both kidneys are completely involved, as they were in this case

The dilated tubules in the illustration may be the distal convolution Failures of continuity can occur at different levels of the nephron

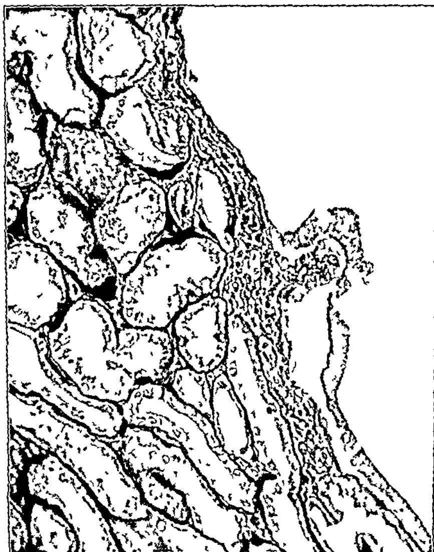


Figure 93

Lining of Congenital Cyst Adult Kidney

The cyst has an epithelial lining which is preserved. The adjacent tissue is not compressed. Congenital cysts can be found in any adult kidney if enough sectioning is done. When cysts are multiple and leave no functioning tissue they produce renal failure. The condition is called polycystic kidney, as it is in infancy (cf. Fig. 92).

One of the striking features of the polycystic kidney is its propensity for infection. Under this condition a cyst or group of cysts may be transformed into sacs of pus. The organisms are the same as seen in pyelonephritis—streptococci and coliform organisms. The shortened life of the patient in a certain number of instances may be due to superadded infection or surgical removal of an infected polycystic kidney.

X rays of these cases show a characteristic picture of an elongated pelvis with shortened calyces. Most cases are easily diagnosed because of the abdominal mass or masses. Subclinical cases, as Bell points out, may have many cysts.* The persisting normal renal parenchyma is sufficient to prevent uremia.

Chapter 13

INCIDENTAL DISEASES THE KIDNEY IN HYPERTENSION IN DIABETES IN AMYLOIDOSIS IN FAT EMBOLISM IN SYPHILIS

HYPERTENSION AND THE KIDNEY

RICHARD Bright s original description of the kidney in chronic renal disease mentioned the association of the enlarged heart with the shrunken kidney Since the introduction of the sphygmonanometer it has been known that cases of arterial hypertension show an enlarged heart This is due to hypertrophy of the left ventricle as revealed by autopsy Shortly after this the kidneys were found to be diseased in many cases of hyper tension [46] Attempts have been made to explain the association between renal d sease and hypertension without complete success

Hypertension is usually defined as persistent elevation of the systolic blood pressure over 150 mm and a diastolic pressure of over 100 in the adult Where an obvious cause for hypertension exists e g chronic renal disease endocrine disorders such as the medullary adrenal tumors or Cushing s syndrome it is called secondary Primary hypertension has no obvious cause The primary variety is divided into the benign and malignant types The renal lesions of malignant hypertension or acute hypertension with renal failure have already been described (p 95)

The remaining problem is benign or essential hypertension Cases which clinically are essential hypertension may include many cases of chronic pyelonephritis frequently with abnormalities of the urinary tract which are obvious with adequate examination [9] Many more will be found to have hyaline arterioles in the kidneys and organs of the splanchnic area The changes present include numbers of obsolescent glomeruli with surrounding atrophied tubules [2] This condition is called Arteriolar Nephrosclerosis Grossly the only remarkable feature is a prominence of the arteries at the arcuate level probably the result of hypertrophy of the intimal elastica (Fig 25)

Despite the fact that all or nearly all of the cases of essential hypertension can be shown to have reduced renal blood flow little kidney change is noted grossly or microscopically in a number of cases It has been suggested that a pressor substance Renin is produced by the ischemic kidney This was described by Tigerstedt and Bergman [92] Goldblatt s experimental work suggests this Renal ischemia is produced by clamping the renal artery and is followed by hypertension in his animals [34] Attempts at demonstration of circulating Renin have been fruitless in cases of essential

hypertension although successful in more acute conditions such as eclampsia[24]

The publication of Goormaghtigh raised hopes for the discovery of an intra renal endocrine like mechanism Granular cells described in the arterioles of the mouse kidney by Ruyter and in the human by Oberling were found in the rabbit and cat by Goormaghtigh[4] Clamping of the renal artery produced hyperplasia of these cells in the rabbit and dog according to Goormaghtigh The granular cells of the renal arteriole were postulated as the site of formation of renin[42]

Examination of human kidneys refutes this consideration PAS methods on frozen or paraffin sections show the granules in admirable fashion when they are present As has been mentioned the granules are present and numerous in the crush kidney regardless of the blood pressure during life in acute hypertension and in cirrhosis of the liver I have not found granules *in normal kidneys* nor in the kidney diseases associated with hypertension The hypothesis of Goormaghtigh does not appear to be substantiated but it has been responsible for many valuable studies

Some evidence indicates that the reduced blood flow through the kidney in essential hypertension is simply part of a general arteriolar constriction It is suggested that those people who develop a persistent hypertension are the same ones who react to pressor tests with exaggerated and perhaps extended hypertension[55] These features make many consider the probability of a nervous mechanism

Participation of the kidney in the production of essential hypertension is being investigated Bell pointed out that arteriosclerosis of relatively conspicuous degree was seen in kidneys of those cases in which hypertension was marked clinically[9] *Arteriolar hyaline may be the renin like* factor Other possibilities will suggest themselves the tubule of the proximal convoluted level especially

Only 10 per cent of the individuals with arteriolar nephrosclerosis develop renal failure Cardiac failure causes death in 50 to 60 per cent Cerebral accidents kill 20 to 25 per cent Those remaining who do not succumb to some unrelated disease will die in renal failure The kidneys are small equal in size and finely granular at autopsy Microscopically these kidneys show a summation of all the different stages of ischemic obsolescence affecting principally the glomeruli with secondary changes in the tubules and interstitial tissues Acute terminations occur with the acute microscopic features present in addition to the chronic ones

DIABETES AND THE KIDNEY

In addition to the intercapillary glomerulosclerosis of Kimmelstiel and Wilson two frequent features of the kidney are seen in diabetes First is the lesion of Armanni or the accumulation of glycogen in epithelial cells of

Henle s loops[6] (Fig 94) The other is acute papillitis or necrosis of the tips of the pyramids[47 97] (Fig 95)

In any disease in which glycosuria is a prominent feature a certain proportion of the glucose is reabsorbed and accumulates in the cells of Henle s loops Typical of this is the glycogen storage disease of v Gierke This is relatively uncommon while diabetes is frequent

In the ordinary Hemotoxylin and Eosin section the affected cells are pale and swollen With the PAS method it is shown that th is due to the presence of carbohydrate (Fig 94) Diastase digestion removes the PAS positive material which is therefore glycogen Actually carbohydrate is present at most levels of the tubule This occurs as globules in the cells of proximal and distal convolutions but is most concentrated and con picu s in the cells of Henle s loops

Necrosis of the tips of the pyramids may be unilateral but is usually bilateral[30] Healed stages are seen but frequently the necrosis appears to have been a terminal event[90] The clinical features are usually overshadowed by acidosis or gangrene of an extremity Occasionally an acute lower urinary tract infection is present with systemic and local features Microscopically and grossly the lesion is what the term necrosis signifies—a loss of vitality of the tip of the pyramid frequently with a line of demarcation (Fig 95) The etiology may be simply an acute and localized pyelonephritis by an organism finding an environment adapted to its multiplication in the diabetic papilla A similar lesion is found occasionally in non diabetics with urinary tract infection[109]

The occurrence of several features of diabetes in one kidney pyramid necrosis and the lesion of Armanni for example is not uncommon On the other hand it is said to be unusual to find intercapillary glomerulosclerosis and the lesion of Armanni in the same case That has been my experience but the significance is not known Necrosis of the tip of a pyramid and intercapillary glomerulosclerosis can occur in one kidney

AMYLOIDOSIS OF THE KIDNEYS

The frequent association of generalized amyloidosis with chronic suppurative foci particularly in bone has been known for many years Cases of renal amyloidosis which are part of a generalized condition appear to have the same etiology Little alteration of renal function is produced in these cases They sometimes show major infiltration of amyloid material into the glomerulus between the muscle cells of the arteries and around the basement membrane of the tubule In rare instances no etiology is determined and the condition is spoken of as primary Its distribution is the same as in the secondary

Occasionally the amyloid is found in a shrunken kidney and the condition has been referred to as the amyloid shrunken kidney[69] This suggests that the amyloid causes the shrinkage The alteration of the albumin

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globulin ratio in the blood which occurs in amyloidosis is seen in some cases of chronic glomerulonephritis Sometimes I have not been sure whether the amyloidosis resulted from the renal disease or vice versa The kidneys containing numerous glomeruli which are loaded with amyloid and associated with atrophied tubules appear to be true cases of amyloid causing renal failure In at least one of these cases I have been struck by the tawny yellow color of the organ grossly and the pigmentation of the tubular cells microscopically

The deposit of amyloid is in relation to the carbohydrate of the basement membrane of the tubule and glomerulus The involvement of the cement substance of the vessels is characteristic It may be that the amyloid material is a normal constituent of the ground substance present normally in minute quantities but increased in the amyloidosis[80] The material on the other hand may be protein precipitated at particular sites with incorporation of carbohydrate The relationship of the disease to antibody formations in experiment animals suggests some role of the globulins[22] Globulin makes up a greater proportion of the urinary protein in renal amyloidosis than in most other diseases[9]

The kidney in marked amyloidosis is firm waxy and keeps its shape well Microscopically when the development of glomerular involvement can be followed it appears that the earliest deposition of amyloid is at the attachment of the arterioles The material is laid down next to the basement membrane (Fig 96) Later it is deposited in the tubular basement membrane



Figure 94

The Lesion of Armanni in a Diabetic Glycogen in the Cells of Henle s Loops

This section was from a diabetic but similar appearances are seen in any prolonged glycosuria The tissue from which the photomicrograph was taken had been fixed in Helly s Fluid (Zenker Formol) This picture shows the preservation of glycogen in an aqueous fixative a fact not realized generally

Glycogen is found as conglomerate spherules in the cells of Henle s loops A similar material is laid down in the basement membrane Like glycogen it can be removed from sections by diastase digestion (*McManus courtesy of Amer Jour Pathology*)

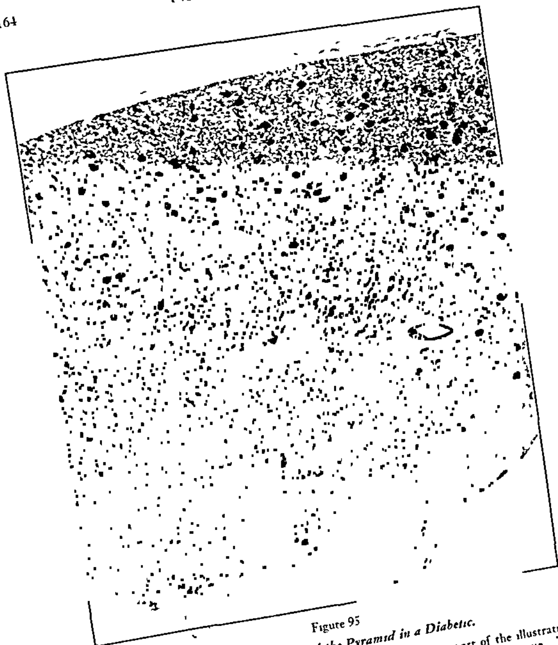


Figure 95

Necrosis of the Tip of the Pyramid in a Diabetic.

The necrotic inner portion of a pyramid is shown in the lower part of the illustration There is a darker line of demarcation between the healthy and the necrotic tissue The glomeruli are conspicuous with the PAS method as they are in kidneys from diabetics The lesion of Armanni (Fig 94) was present but is not recognizable at this magnification

The necrosis of the tip of the pyramid is an acute pyelonephritis It is not uncommon in diabetes It is seen in non-diabetics in association with urinary tract obstruction



F gure 96

Glomerulus i i Renal Amyloidosis

I e glomerulu has an nfil at ng substance accen uat ng the cap llary loc ps Th s substance conta ns carbohydrate and colors v h PAS It s mo e b ttle than bas ment mem brane Fractures are produced n sect on ng There s sl ght nfiltra on of the arter ole and ome th cken ng of s me tubular basement n embranes

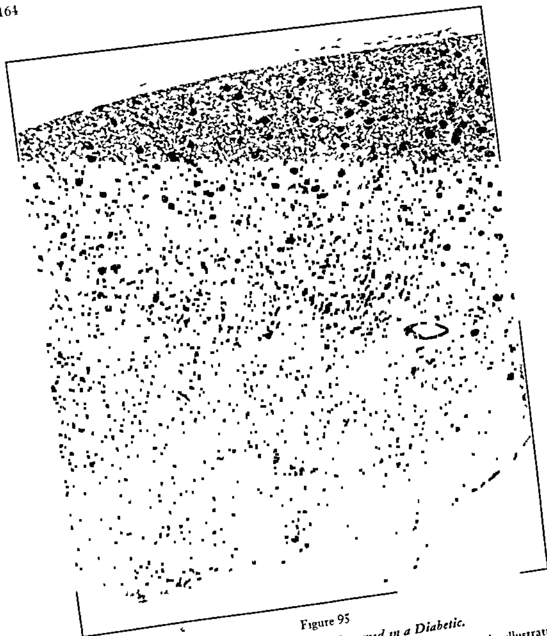


Figure 95

Necrosis of the Tip of the Pyramid in a Diabetic.

The necrotic inner portion of a pyramid is shown in the lower part of the illustration There is a darker line of demarcation between the healthy and the necrotic tissue The glomeruli are conspicuous with the PAS method as they are in kidneys from diabetics The lesion of Armanni (Fig 94) was present but is not recognizable at this magnification

The necrosis of the tip of the pyramid is an acute pyelonephritis It is not uncommon in diabetes It is [illegible] in non-diabetics in association with urinary tract obstruction



Figure 96

Glomerulus in Renal Amyloidosis

The glomerulus has an infiltrating substance accentuating the capillary loops. This substance contains carbohydrate and colors with PAS. It is more brittle than basement membrane. Fractures are produced in sectioning. There is slight infiltration of the arteriole and some thickening of some tubular basement membranes.



Figure 99

Fat Emboli in Glomeruli

Fat embolism or traumatic lipemia most commonly follows fractures of the long bones Occasionally it is seen following trauma to subcutaneous tissues More recently it has been described in sickle cell anemia and in gas gangrene The mechanism of production in fractures seems to be the pooling of the marrow fat and its suction into an open vein In other conditions the causative sequence is a matter of speculation

The fat dilates the glomerular capillaries It is lost in the process of paraffin imbedding The capillaries appear empty and dilated Renal failure is not produced I have seen hypertension appearing in massive glomerular fat embolism

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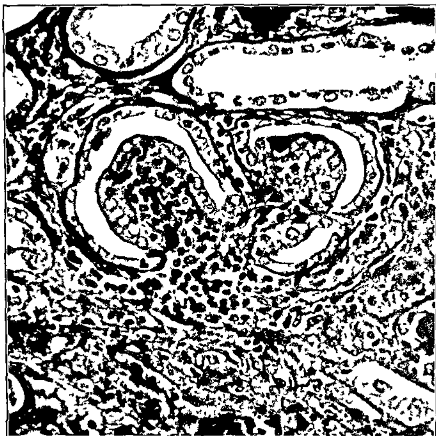


Figure 100

Syphilitic Lesion in Kidney

[illegible]

to find syphilitic lesions in the rest of the body

The syphilitic lesion of Rich consists of foci of lymphocytes herniating into the tubules as shown above

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